From the Department of Clinical Sciences, Danderyd Hospital
Division of Rehabilitation Medicine
Karolinska Institutet, Stockholm, Sweden

ASSESSMENT AND MANAGEMENT OF PATIENTS AT RISK FOR PERSISTING DISABILITY AFTER MILD TRAUMATIC BRAIN INJURY

Giedrė Matusevičienė

Karolinska Institutet

Stockholm 2018

All previously published papers were reproduced with permission from the publisher.
Cover art: M.K. Čiurlionis “The Past” 1907, ČDM Čt-210, M.K. Čiurlionis National Museum of Art, Kaunas, Lithuania
Published by Karolinska Institutet.
Printed by Eprint AB 2018

ISBN 978-91-7831-030-2

Assessment and management of patients at risk for persisting disability after mild traumatic brain injury

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Giedrė Matusevičienė

This thesis will be publicly defended in lecture hall Hjärtat, Karolinska Institutet, Danderyd Hospital, on June 15, 2018, at 10:00 AM

Principal Supervisor:
Dr. Catharina Deboussard
Karolinska Institutet
Department of Clinical Sciences
Division of Rehabilitation Medicine

Co-supervisors:
Dr. Alison Godbolt
Karolinska Institutet
Department of Clinical Sciences
Division of Rehabilitation Medicine

Professor Jörgen Borg
Karolinska Institutet
Department of Clinical Sciences
Division of Rehabilitation Medicine

Opponent:
Professor Niklas Marklund
Lund University
Department of Clinical Sciences,
Division of Neurosurgery

Examination Board:
Professor Birgitta Bernspång
Umeå University
Department of Community medicine and rehabilitation
Division of Occupational Therapy

Associate Professor Rune Brautaset
Karolinska Institutet
Department of Clinical Neuroscience
Division of Eye and vision

Associate Professor Martin Fahlström
Umeå University
Department of Clinical science
Division of Professional Development

To my family

ABSTRACT

There is a lack of evidence-based interventions for patients with persisting problems after mild traumatic brain injury (mTBI). The interventions needed should focus on patients at particular risk for persisting disability after mTBI and target modifiable factors. After initial studies of an early educational intervention unexpectedly gave negative results (studies I, II), a renewed focus on possible targets for interventions was needed: studies III, IV explored associations with self-reported and objectively measured visual disturbances, self-rated and objectively measured fatigue, and correlations between fatigue, visual functions and attention.

Study design and participants: Randomized controlled intervention study (studies I, II), and exploratory prospective observational study (studies III, IV). In studies I, II, patients with an estimated high risk for persisting disability were randomized to an early interventional visit (EIV) to physician or to Treatment as usual (TAU). All 173 patients, including the non-randomized group were followed up at 3 months after the injury. Studies III, IV, compared patients with mTBI to patients with minor orthopedic trauma and non-injured controls, with 15 in each group. Participants were assessed sub-acutely and after approximately 3 months.

Outcome measures: Multimodal outcome measures related to the ICF-framework incorporating: 1.Self-reported data on symptoms (Rivermead Post Concussion Symptoms Questionnaire (RPQ)), activity and participation (Occupational Gap Questionnaire, Rivermead Head Injury Follow-up Questionnaire), and quality of life (SF-36) (studies I, II). 2. Findings from visual examination (accommodation, convergence, visual acuity, saccades), and visual symptoms (Convergence Insufficiency Symptoms Survey (CISS) and RPQ (study III). 3. Self- reported data on fatigue: acquired fatigue, (RPQ-f), and trait fatigue (Fatigue Severity Scale) and objectively measured cognitive fatigability (DSST-f) and saccades (study IV).

Results: The intervention was not found to have an effect on symptoms, activity, participation or quality of life (studies I, II). Patients with few symptoms early after the mTBI continued to report few problems at follow-up. Visual findings showed that accommodative amplitude was lower in the mTBI group compared to non-injured controls at sub-acute stage; near point of convergence in the mTBI group was receded at sub-acute stage, but improved at follow-up; patients with mTBI reported a higher CISS score than persons in the control groups (study III). Acquired fatigue was present more often after mTBI and correlated to cognitive fatigability. Associations were found between acquired fatigue and some saccade measures, but not with other visual measures.

Conclusions: An early intervention to patients at risk for persisting disability had no effect on symptoms, activity, participation or quality of life. Patients with few symptoms early after mTBI are likely to have a good outcome. Some transient measurable visual changes regarding convergence were found in patients with mTBI during the sub-acute period after the injury. Some support for the suggested value of assessing different aspects of fatigue have been found.

LIST OF SCIENTIFIC PAPERS

I. Matuseviciene G, Johansson J, Möller M, Godbolt AK, Pansell T, Deboussard CN.Early intervention for patients at risk for persisting disability after mild traumatic brin injury: A randomized, controlled study. BMJ Open. 2018 Feb 3;8(2), doi: 10.1136/bmjopen-2017-018734.

II. Matuseviciene G, Eriksson G, DeBoussard CN. No effect of an early intervention after mild traumatic brain injury on activity and participation: A randomized controlled trial. J Rehabil Med. 2016 Jan;48(1):19-26, doi: 10.2340/16501977-2025.

III. Matuseviciene G, Johansson J, Möller M, Godbolt AK, Pansell T, Deboussard CN. Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden: an exploratory prospective observational study. BMJ Open. 2018 Feb 3;8(2), doi:10.1136/bmjopen-2017-018734.

IV. Möller MC, Matuseviciene G, Johansson J, Pansell T, Nygren Deboussard C. Self-rated fatigue and cognitive fatigability: associations with saccade performance and attention after mild traumatic brain injury – an exploratory prospective observational study. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ACRM	American Congress of Rehabilitation Medicine
ADA	Automatic Detection Accuracy
ADL	Activities of Daily Living
ADS	Automatic Detection Speed
AI	Accommodation Insufficiency
ANOVA	Analysis of Variance
ASL	Antisaccade Latency
CBT	Cognitive Behavioral Therapy
CI	Convergence Insufficiency
CISS	Convergence Insufficiency Symptoms Survey
CONSORT	Consolidated Standards of Reporting Trials
CRASH	Corticosteroid Randomization After Significant Head injury
CSA	Controlled Search Accuracy
CSS	Controlled Search Speed
CT-scan	Computerized Tomography scan
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DSST-f	cognitive fatigability calculated with results from the DSST
DTI	Diffusion Tensor Imaging
ED	Emergency Department
EIV	Early Intervention Visit
fMRI	functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
GCS	Glasgow Coma Scale
GFAP	Glial Fibrillary Acidic Protein
GOSE	Glasgow Outcome Scale Extended
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases
ICF	International Classification of Functioning
LOC	Loss Of Consciousness

MCS	Mental Component Summary
MRI	Magnetic Resonance Imaging
mTBI	mild Traumatic Brain Injury
NPC	Near Point of Convergence
OGQ	Occupational Gaps Questionnaire
PCS	Physical Component Summary
PFV	Positive Fusional Vergence
PSL	Prosaccade Latency
PTA	Post Traumatic Amnesia
QoL	Quality of Life
RAF-rule	Royal Air Force rule, for accommodation measurements
RCT	Randomized Controlled Trial
RHFUQ	Rivermead Head Injury Follow-Up Questionnaire
RPQ	Rivermead Post Concussion Symptoms Questionnaire
RPQ-f	fatigue question on RPQ
rs-fMRI	resting state functional MRI
SD	Standard Deviation
S100-B	Calcium binding protein B
SF-36	Short Form Health Survey
SLDT	The Swedish Lexical Decision Test
TAU	Treatment As Usual
TBI	Traumatic Brain Injury
UCH-L1	Ubiquitin C-terminal Hydrolyze L1
WAIS-III	Wechsler Adult Intelligence Scale

1 INTRODUCTION

Head injury can happen to anyone at any time, resulting in traumatic brain injury (TBI) of varying severity. TBI is a substantial public health problem and is one of the most common neurological conditions that affect functioning of people of working age (1). Traumatic brain injury is categorized into mild, moderate and severe according to the scores of Glasgow Coma Scale (2). Generally, traumatic brain injury is classified as severe, if GCS score is 8 or less, moderate if GCS score is 9-12, and mild if the GCS is 13-15. The largest part, 70 - 90% of traumatic brain injuries are mild (3). Prognosis for mild traumatic brain injury (mTBI) is often good (4), but a minority of patients report long lasting problems (5-12) and the clinical course and outcomes are variable. Given the high incidence of mTBI, even a small proportion of patients with persisting symptoms and disability after mTBI represents a large number of people. The long-term consequences involve both individual suffering and increased costs for society, primarily by means of increased consumption of health care (13). Interventions after mTBI should target those patients that are at risk for persistent symptoms (14).

Despite growing evidence from mTBI research, there is still a lack of knowledge in prediction, prognosis and treatment of this heterogeneous condition. Therefore, the search is ongoing for objective methods for assessment and monitoring recovery after mTBI.

1.1 DEFINITION OF MILD TRAUMATIC BRAIN INJURY

There is variety of criteria used to define mTBI (15, 16). World Health Organization (WHO) Collaborating Center Task Force on Mild Traumatic Brain Injury have recommended a definition of mTBI for research use (17), that is based on the definition provided by Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM) (18): “mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by a penetrating craniocerebral injury” (17).

Most of the patients with mTBI do not have visible abnormalities on neuroimaging (19). Prevalence of neuroradiological abnormalities, such as, bleeding or swelling is estimated according to GCS, ranging from 5% for those with GCS 15 to 30% with GCS 13 (20).

Most mTBI research is conducted in civilian population, but there are two other related mTBI research areas: sports-related concussion (21) and mTBI caused by the exposure of military

personnel to blasts (22). Terminology related to mild head trauma is diverse, and the terms "Mild traumatic brain injury" and "concussion" are used somewhat interchangeably, with "concussion" being more often used in relation to sporting injuries. The recent sport related concussion conference concluded that "the lessons derived from non-sporting mTBI research informs the understanding of sport-related concussion (and vice versa), and this arbitrary separation of sporting versus non-sporting TBI should not be viewed as a dichotomous or exclusive view of TBI" (21).

1.2 EPIDEMIOLOGY

The incidence of hospital treated patients with mTBI in the Western countries is between 100 to 300 persons per 100,000 inhabitants (3). Most of the mTBI are caused by falls, motor vehicle accidents followed by sports injuries (3, 23). In the latest decades, rates of hospitalization after mTBI in Sweden are decreasing, from approximately, ~17,000 in 1998 to ~10,000 in 2008. According to recent statistics report from Swedish National Board of Health and Welfare, in 2014-2016, the annual incidence of hospitalization of patients with mTBI in Sweden decreased to 6,690 (24). The probable reason for the reduced number of hospitalizations after mTBI in Sweden is an introduction in 2006 of the clinical guidelines (25) for the routine use of computed tomography scan (CT-scan) examination in diagnosing mTBI in acute stage (26). Regarding visits to emergency departments (ED) due to mTBI in Sweden, the number of registered visits in 2010 was 21,700 in all age groups (0 to >80 years) (27). That comprised 231 persons per 100,000 inhabitants. The highest incidence rates were in age groups 0-14 years and > 80 years. Most of the individuals presenting to ED were men (27). A considerable number of patients with mTBI are not seeking medical care, and thus, are not included in hospital or ED registers, which might imply that the incidence may be much higher, up to an estimated 600 persons per 100,000 (3). Consequently, the genuine incidence of mTBI is difficult to determine partly due to a lack of the objective diagnostic testing, and heterogeneity of definitions of mTBI in the studies (28).

1.3 MILD TRAUMATIC BRAIN INJURY AND INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH (ICF)

The ICF is a classification system, which provides a standardized conceptual basis for definition and measurements of functioning and disability (29). The ICF framework includes the following components: body structure and functioning, activity and participation, and environmental and personal factors (29). Functioning after a disease or injury and disability is presented as a complex interaction between health condition, personal factors and circumstances surrounding the individual. The ICF concept is a useful tool for measuring the consequences of such clinical conditions that do not have established objective measures during the recovery, such as mTBI or chronic pain.

The ICF serves as reference system during all phases of neurorehabilitation: from diagnosis setting to the assessment of rehabilitation needs, goal setting, interventions and outcome

measuring (30). The ICF can be used in each of these phases in order to create an individualized plan for rehabilitation.

The ICF concept has in a qualitative study by Sveen et al 2013 been found to be useful in describing problems related to mTBI (31). This study described that most reported functions were related to cognitive and emotional domains of symptoms, frequently reported impairment of activities and participation, concerned daily routines and work. Reported environmental factors included health care services, social security system, social network and attitudes towards injured persons.

1.4 ASPECTS RELATED TO BODY STRUCTURE AND FUNCTIONING

1.4.1 Pathophysiological mechanisms

Impact on the brain of biomechanical force includes linear and rotational acceleration components (16, 32). After the impact of biomechanical force to the head, the primary injury is induced to the neuronal bodies and axons, often also causing intracranial hemorrhages (33). Directly after the primary injury, a cascade of metabolic processes starts causing secondary injury (34). The knowledge of biomechanical and neurometabolic processes after TBI is mostly based on results from experimental research on animal models (35). As a response to metabolic changes, neuroinflammation is initiated (36). Neuroinflammation is thought to have both positive and negative components, which are also likely to differ between the acute and chronic phase of brain injury (34). Neuroimmunological response to trauma can be seen as being beneficial, like a wound healing process, including “cleaning” of the cellular debris, restoration of brain tissue homeostasis and preservation of the blood-brain barrier (34). A mild acute inflammation is likely to be required for stimulation of neurogenesis, or healing (16). At the same time, neuroinflammation that becomes chronic can be disadvantageous for the healing process. For most of mTBI cases the neurometabolic changes are reversible (16).

Biochemical blood tests have been suggested as biomarkers for diagnosing and tracking recovery after mTBI. One established biochemical marker is a calcium binding protein S-100B, found in astroglial cells after mTBI (37). S-100B has, however, a low specificity, due to the extracranial release, and has been found in the blood of patients with orthopedic trauma (38), and in healthy individuals after sports activities (39). Recently, a combination of two biochemical blood biomarkers, glial fibrillary acidic protein (GFAP), found only in astrocytes in central nervous system, and ubiquitin C-terminal hydrolase L1 (UCH-L1), found in neuron cytoplasm, also expressed in endothelial and smooth muscle cells (40), was recognized as a diagnostic test by FDA (Food and drug administration in USA) (41). This test showing high sensitivity and specificity, can rule out individuals with a low risk of intracranial injury and those who do not need a brain CT-scan (41).

Dynamic changes in the brain that vary with time after the injury, could be detected by diffusion tensor imaging (DTI) demonstrating changes in microstructural integrity of white matter tracts (42). Functional magnetic resonance imaging (fMRI) and resting state functional MRI (rs-fMRI) detect changes in functional connectivity of the brain networks (43). Recent

studies have shown altered activation of brain networks in patients with mTBI (44, 45), and some associations with persisting symptoms at 3 months after injury (46).

1.4.2 Symptoms

Symptoms after mTBI are often divided into the following groups: somatic (headache, dizziness, nausea/vomiting, sleep disturbances, noise sensitivity), cognitive (deficits in attention, executive problems, pure memory, taking longer to think) and emotional/affective symptoms (emotional instability, irritability, feeling depressed, restlessness). The visual symptoms, such as double vision and blurred vision, are often attributed to somatic symptoms group.

Symptoms after mTBI are often regarded as post-concussion symptoms and are categorized by two different sets of criteria, both criticized for the lack of specificity to mTBI (4): Postconcussional syndrome according to the International Classification of diseases, 10th edition (ICD-10) (47) and Postconcussional disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (48). In Postconcussional syndrome, a history of head trauma with LOC and three symptoms should be included from different symptom categories, among others, headache, dizziness, fatigue, irritability, reduced tolerance to stress and alcohol, fear of permanent brain damage (47). Postconcussional disorder has more stringent criteria and requires head trauma, three of the symptoms that last at least 3 months, such as being easily fatigued, headache, dizziness, anxiety, or depression, in addition to evidence from neuropsychological assessment of difficulties in concentrations, memory and attention, and decline in social and occupational functioning (48). The new Diagnostic and Statistical Manual of Mental disorders (DSM-V) does not any longer include a category “postconcussional disorder”, and has instead introduced a new category “Major, or mild neurocognitive disorder due to traumatic brain injury” (49).

Although most of the symptoms after mTBI are attributed to the brain injury, most of the complaints are non-specific and are also reported after other non-head injuries or chronic pain (50), and are even present in the general population (51). Several studies showed that trauma controls with injuries other than to the head report similar symptoms to patients with mTBI (52, 53). The same symptoms might also occur in many other conditions, without a head injury, such as anxiety or depression (54-56). There is no consistent difference between mTBI and trauma patients in the sub-acute phase; therefore, it was proposed to replace the term post-concussion with post-traumatic (57). However, several longitudinal controlled studies showed differences in the frequency and nature of reported complaints between patients with mTBI and trauma controls, with more severe complaints in the mTBI group (58-60). A recent systematic review of mTBI has suggested that other factors unrelated to injury influence the persistence of symptoms: injury-related psychological stress, poor premorbid physical and psychiatric health (57). Co-morbidities, such as anxiety at the time of injury and one week after the injury have been shown to predict post-concussion symptoms at three months after mTBI (52). Personality traits and psychological vulnerability have been suggested to contribute to long-term complaints after mTBI (61). Female gender is shown to be a risk

factor for long-term symptoms (62-64). Litigation and seeking compensation are also related to persistent symptoms (4, 65).

1.4.3 Specific aspects: vision and fatigue

Vision

Visual symptoms are part of self-reported complaints after mTBI, and include double or blurred vision, eyestrain, and sensitivity to light. Visual networks are widespread throughout the brain, and trauma to the head, as in mTBI, can disrupt integrity of the fragile functional network (66-69). Recent studies show associations between findings in assessments of oculomotor functions and changes in neuroimaging, both with diffusion tensor imaging (70), and with fMRI (68). Vision plays a vital part in connecting people with the surrounding world and therefore even minor visual disturbances after mTBI can cause problems in everyday activities. Therefore, a sudden change in visual functioning after mTBI might impact activities that involve visual tasks requiring efforts and concentration, such as computer work or reading, with particular difficulties in following the text line or un-intentional jumping over a word.

Previous studies have shown a high prevalence, up to 70%, of various visual changes in individuals with visual complaints after mTBI (71-73), compared to less than 10% in the otherwise healthy pre-presbyopic population with visual symptoms (74-76). Changes in oculomotor-based vision functions, namely, accommodation, convergence and the generation of saccades, presented in patients with mTBI both in civilian and military settings (71, 77-79) (see Glossary of terms for visual functions and assessments).

Deficiencies in convergence are the most reported oculomotor changes after mTBI, including receded near point of convergence (NPC), and have been shown in retrospective and controlled studies (71, 72, 78). Convergence insufficiency (CI) might be one of the reasons for visual symptoms after mTBI such as blurred or double vision or impaired work at near (73). Reduced fusional vergence, a reduced ability to keep eyes in alignment and maintain clear single vision could be another reason for blurred vision after mTBI (80). Another vision problem that is found in patients with mTBI is deficits in accommodation with impaired focusing at near or at a distance (81, 82). The accommodative abilities generally deteriorate with age, and at 40-45 years of age most of the individuals have presbyopia, difficulties in focusing on near objects.

Changes in saccade generation parameters have been shown in several studies (72, 77, 78, 83, 84). Saccades are fast eye movements elicited to re-fixate from one point to another. There are several types of saccades: visually guided saccades, such as prosaccades, rapid eye movements towards objects suddenly appearing in the visual field; and volitional saccades, such as antisaccades, that involve cognitive processing with inhibition of reflexive response and intentional engaging of attention and spatial memory. Previous studies indicate that antisaccades might be effective measures to distinguish patients with mTBI from controls, indirectly showing cognitive deficits after mTBI (70, 77, 85).

Assessment of oculomotor changes has been proposed as a method for diagnosing and monitoring the recovery following mTBI and as a possible biomarker after mTBI (70, 86). Most of the studies of visual changes after mTBI include patients with visual complaints in later stages, several months or years after the mTBI. There are few prospective studies investigating relationship between visual complaints and objective assessments of vision functioning in acute and sub-acute stage after mTBI (84, 87).

Glossary of terms related to visual assessments

Accommodation	The process by which the eye adjusts its refractive power to maintain a clear image on the retina when focusing on objects at different distances. Accommodative disorders affecting these functions may lead to blurred vision at near and a delay in clarity of vision when alternating between near and far.
Near point of accommodation	Measures how close an object can be brought while still maintaining a clear image.
Accommodative facility	Measures the flexibility of accommodation, i.e. to alternately exert and relax accommodation.
Convergence	An ability to move the eyes simultaneously and horizontally in opposite directions to follow an object as it moves in depth. Deficiencies of convergence may lead to double vision at near.
Near point of convergence (NPC)	The point, where the eyes achieve maximum convergence while still maintaining single vision.
Fusional vergence	An alignment of the eyes in order to provide a clear single vision. Impaired fusional vergence can cause blurred or double vision.
Stereo acuity	A test for grading the ability to detect depth differences, stereoscopic vision. Stereoscopic vision requires simultaneous binocular visual input.
Saccades	Fast eye movements elicited to refixate from one point to another that can be performed under both reflexive and voluntary control.

Fatigue

Fatigue is not a unitary phenomenon, and no exact definition of fatigue exists (88). Fatigue is described as perceived lack of physical and mental energy that interferes with daily activities, or a diminished capacity to accomplish an activity (88, 89). Brief periods of fatigue are estimated to occur in 15-25% of the general population (90). Fatigue is one of the most frequently reported symptoms after mTBI (7-9, 58) and is associated with poor outcome (9,

91). Existing evidence shows that self-reported fatigue decreases over time after mTBI, but some patients continue reporting persisting fatigue (92).

Results of self-rating of fatigue have been found to be hampered by confounding from co-existing problems such as anxiety, depression, sleep disturbances or pain (93, 94). Fatigue has also been shown to be associated with reduced psychomotor speed (95) attention function (96) and executive functions (97).

There is a lack of consistency in the definition of fatigue and also the use of different assessments for investigating fatigue in mTBI (93). Several different scales have been developed for the assessment of fatigue from different perspectives, such as frequency, severity, impact on functional outcome, and time period over which the respondents rate their fatigue.

A definition of trait fatigue, or general fatigue is proposed for measuring the extent of perceived fatigue over time, and state fatigue, for fatigue at the moment (93). One of the scales for measuring trait fatigue is the Fatigue Severity Scale (FSS), assessing general fatigue and its consequences on daily functioning during (98).

In order to introduce an objective fatigue measure, a standardized taxonomy for fatigue was proposed, differentiating the perception of fatigue, as a subjective concept, and performance fatigability, which could be objectively measured (88).

Few previous studies have shown the relationship between self-reported fatigue and objectively measured cognitive fatigability, e.g. by objectively measuring a decreased performance over time during a sustained complex information processing task (93, 99).

1.5 ACTIVITY AND PARTICIPATION

According to the International Classification of Functioning, Disability and Health (ICF), activity is described as a task or action performed by an individual. Activity limitations are difficulties experienced by an individual in performing activities of daily living (29). Studies of mTBI have shown that more symptoms early after the injury correlate with more symptoms and changes in everyday activities 3 months after the injury (7, 12). Moreover, patients with perceived cognitive deficits after mTBI have been found to experience limitations in their daily activities (58). Long lasting symptoms after mTBI might contribute to the limitations in the person's social, recreational life, and work disability (5, 100). One of the goals of rehabilitation is participation, defined as person's involvement in a life situation (29), sometimes even despite the fact that there are long-lasting symptoms due to an injury or disease. Restrictions in participation might lead to life that is less diverse (101).

1.5.1 Sickness absence

International Classification of Functioning, Disability and Health had emphasized that work performance and return to work are very important outcome measures and key elements in rehabilitation (29). Studies of sickness absence and return to work after mTBI are few and

have reported divergent results (4, 102). The varying results of these studies might be due to differences in mTBI definition and in patient selection and characteristics (102). Existing evidence shows that most of the individuals return to previous occupations 3-6 months after the injury (7, 102-104). Sickness absence of less than two weeks in more than 50% of patients with mTBI was reported in a Finnish study that included 109 patients (104). The majority of them, 93%, ended their sick leave within 3 months. In one Swedish study, 75% of patients with mTBI had a sickness absence length of less than 10 days, 20% of patients were on sick leave up to 30 days, and only one person did not return to work three months after the injury (7). Another Swedish study revealed that 15% of patients with mTBI still were on sick leave one year after mTBI (105). Previous studies showed that patients with mTBI reported greater effort and more fatigue related to return to work after the injury (106) compared to a trauma control group. However, rates of patients with mTBI that returned to work did not show a difference from a trauma control group (58).

1.6 PERSONAL FACTORS

Mild traumatic brain injury is a traumatic event for the person sustaining the injury, indicating that there is a psychological distress involved. Persisting symptoms after mTBI are difficult to compare between individual patients despite the similar severity and injury mechanisms (11). Given the importance of distinguishing those patients at risk for persistent complaints, vulnerability to traumatic events can be a factor to consider (107).

One of the factors influencing response to traumatic events that has been suggested is psychological coping, e.g. psychological adaptation to stress or important life events (108). There are different strategies of coping – active, e.g. problem-solving, and passive, or maladaptive, which is associated with negative emotions such as worrying (108). A negative illness perception in combination with maladaptive coping strategy might lead to anxiety and depression, and in that way, sustain post-concussion symptoms (61, 109, 110).

1.7 QUALITY OF LIFE

The WHO describes quality of life of each individual as “perception of ones position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (111).

Health-related quality of life (QoL) lies outside the ICF framework, but plays an important part in the comprehensive assessment of patients with mTBI (61, 109). Health- related QoL instruments measure different dimensions, such as physical, psychological, social and daily life (112). The instruments used in assessment of activity and participation overlap partially with health-related QoL measures (113). The latter, however provide an important extra dimension in assessing the subjective experience of a person’s problems and the degree to which they are bothered by the problems (113).

In previous studies, reduced quality of life correlated with a high number of post-concussion symptoms 3 months after injury (100). Quality of life and emotional functioning after mTBI

were shown to be associated with pre-injury coping styles (109). Patients with mTBI with avoidant coping strategies had worse emotional functioning and reported a lower QoL (109).

1.8 TOWARDS HOLISTIC APPROACH: BIOPSYCHOSOCIAL MODEL

In order to understand persisting symptoms and poor outcome after mTBI, one has to take into account multiple biological, psychological and social factors that influence the recovery process. A biopsychosocial model is proposed as a concept for poor outcome after mTBI comprising pre-, peri, and post-injury factors influencing recovery after mTBI (114). Reporting of post-concussion symptoms depends on the individual, and represents an accumulation of a myriad of variables, such as current life stress, genetics, personality factors, history of mental health and other medical problems as well as different psychosocial factors.

The biopsychosocial approach can help to guide clinical management in ruling out alternative diagnoses and explanations for persisting problems (114, 115). This includes careful documentation of the nature and course of symptoms, the history of previous medical conditions and mood disorders, clinical examination neurological domains, cognition and vision and an estimation of potential influencing factors, such as psychosocial situation, malingering, secondary gain (116). Clinical recommendations that include the biopsychosocial approach might help to guide clinicians towards the right areas of interventions for persisting problems after mTBI.

1.9 CLINICAL COURSE

1.9.1 Recovery after brain injury in general

Recovery from a traumatic brain injury in general varies depending on the individual and on the type and severity of brain injury. Patients can have impairments in physical, cognitive and emotional functioning as a consequence of the injury. Attempts at predicting the degree of TBI recovery remain crude. Recovery can be seen months, and even years, after the initial injury. Some indicators of prognosis after TBI are considered to be important: duration of coma or loss of consciousness, duration of post-traumatic amnesia, GCS and age (117).

There are some prediction models that have been suggested as being useful in clinical practice. One of these is the CRASH model for moderate and severe TBI (117), that estimates the risk of mortality at 14 days and death/severe disability at six months after the injury based on country, age, GCS score, pupils reaction to light, major extra-cranial injury and CT-scan findings.

Recovery of brain function is thought to occur by several neuroplastic mechanisms (118, 119). Some neuroplastic mechanisms are activated early after the injury, and some continue their effect even in the chronic stage (120). Neuroplasticity also plays an important role in the re-learning of lost skills or in acquiring new compensatory skills (119). Understanding the natural course of recovery and neuroplastic mechanisms after TBI is important for planning

interventions (120). The natural history of recovery after brain injury can help to navigate between the problems that are known to be resolved naturally (initial confusion, pain), and possible complications (hydrocephalus) (115).

1.9.2 Clinical course of mild traumatic brain injury

Despite extensive research in neurophysiology, biomechanics and clinical presentation, there are still gaps in our understanding of the course of recovery after mTBI. One of the possible explanations could be that there are no established objective measures correlating with symptom presentation and limitations in daily activities. The systematic review by the International Collaboration on Mild Traumatic Brain Injury on self-reported prognosis after mTBI 2014, a follow-up of the WHO taskforce 2004, concluded that symptoms reported after mTBI are mostly transient and are resolved within days to weeks after the injury, and most of patients recover over one year (4, 57).

Cognitive impairment has been found to be common up to 2 weeks after mTBI, with a rapid improvement (52, 121). A meta-analysis and prospective studies on cognitive functioning after mTBI concluded that patients with mTBI have no longer impact on global cognitive functioning at 90 days after mTBI (19, 122).

There are no established phases during the time of recovery after mTBI. Studies of mTBI report an outcome at different time periods after the injury: 2-3 weeks, 1, 3 or 6 months after mTBI. Generally, time period of one to three days after mTBI is called acute phase; some studies define even 1 week as acute post-injury phase after mTBI (6, 123). The time period up to 3 weeks or one month is defined as sub-acute phase and thereafter – the chronic phase. Objective assessment of patients with mTBI is important both at the proximal and at the distant end of the recovery process (116).

Monitoring the recovery after mTBI is based extensively on self-reported injury events and post-injury symptoms. Several potential biases and confounders during the recovery should be accounted for after mTBI: imprecise recall of duration of loss of consciousness (LOC) or post-traumatic amnesia (PTA) and injury severity; the impact of acute stress on symptom reporting; influence of comorbid conditions, such as pain and substance abuse; inaccurate self-estimation of pre-injury functioning, psychosocial considerations that arise after the injury and that are automatically self-attributed to mTBI; the influence of comorbid conditions such as anxiety or depression (28, 124).

1.10 CLINICAL MANAGEMENT OF MILD TRAUMATIC BRAIN INJURY

1.10.1 Acute management

The most important issue in the early management of mTBI is to recognize neurological symptoms and signs that increase the risk of acute deterioration.

There are two major complications after mTBI: delayed hemorrhage and delayed swelling of the brain. Initial examination and decision-making about the severity of brain injury

according to GCS might be compromised by intoxication with alcohol or drugs. Neurological signs, such as pupillary response to light, and brain imaging are not sensitive to intoxication (42, 125). Common structural imaging methods for mTBI are CT-scan, performed acute, on the day of the injury, and MRI, usually performed sub-acute, up to 3 weeks after the injury. MRI has shown intracranial changes, such as hemorrhages and axonal injuries in 27% of the patients with mTBI, despite normal acute CT-scan on admission (42).

In order to improve neurotrauma care, the evidence-based Scandinavian guidelines for initial management of minimal, mild and moderate head injury for adult patients were updated including CT-scan selection, admission and discharge (126). Patients presenting with GCS 13 are regarded here as patients with moderate traumatic brain injury. These patients have to undergo a CT-scan, they have to be admitted for observation, and a physician has to consider consultation with a neurosurgeon. The same recommendations apply to patients presenting with GCS 14-15 and having additional risk factors, such as post-traumatic seizures, neurological deficits or treatment with anticoagulants. Patients with GCS 14 and 15 with no risk factors and serum biomarker S100B ≤ 0.1 within 6 hours after the injury could be discharged home. A new category, minimal traumatic brain injury, is introduced defining patients presenting at ED with GCS 15 and no additional risk factors that could mean a discharged home. It is recommended to provide all patients with written information at discharge (126).

1.10.2 Interventions later after injury

Given the generally good recovery after mTBI, it is suggested that follow-up should focus on those patients who have a high risk for a poor outcome (14). Interventions after mTBI are facing two important challenges: to identify patients at risk early after the injury in order to prevent chronification of complaints, and to identify targets, e.g. prognostic modifiable risk factors, for poor outcome that are important for secondary prevention, aiming to address persisting symptoms and improving outcome (114).

The existing evidence, presented in systematic reviews, shows that an early intervention that includes educational and reassuring information is beneficial to recovery after mTBI (14, 127, 128).

Written information about mTBI and scheduled telephone calls with structured individualized educational information at 2 days and at 2, 4, 8, and 12 weeks after the injury gave a reduction in post-concussion symptoms at 6 months compared to the control group (129). No difference between the groups was found regarding general health.

A different approach on structured information has been investigated in a study where short text messages were sent 3 times daily to patients with mTBI during a period of 1 to 14 days after discharge from ED (130). Patients with mTBI showed improvement with fewer and less severe post-concussion symptoms, but no statistically significant difference was found compared to controls at two weeks after the injury (130). A recent randomized controlled interventional study used another novel approach, such as web-based information provided

for patients with mTBI in a military setting, and found no difference between intervention and controls groups (131).

Multidisciplinary outpatient interventions have not given any improvement in outcomes (105, 132, 133). In a recent randomized controlled trial (RCT), an intervention consisting an outpatient follow-up program was offered to the group of patients with persisting symptoms 6-8 weeks after mTBI compared to a control group that was followed-up by a general practitioner (133). This intervention had no effect on return to work, but it was a trend for improvement regarding post-concussion symptoms in the intervention group.

Clinicians have to rule out alternative medical conditions and explanations that may account for long-lasting problems after mTBI. Recent studies of mTBI indicate that psychological and psychiatric conditions, closely related to post-concussion symptoms, might be targets for treatment in order to improve the outcome after the injury. Psychological interventions, such as cognitive behavioral therapy (CBT) have been addressed as treatment for patients with mTBI (134, 135). A recent randomized controlled trial compared CBT to telephone counseling targeting patients with many symptoms early after mTBI (136). Patients were not presented with written information. Treatments started 4-6-weeks after mTBI and included five sessions of CBT intervention or five phone consultations in time period between 4 and 8-10 weeks after the injury. Patients in the telephone counseling group had fewer symptoms at 3 and 12 months after the injury, and more patients in this group showed a full recovery, according to the Glasgow Outcome Scale Extended (GOSE) compared to patients who received CBT (136).

The benefit of bed rest early after mTBI has been investigated in an RCT. No effect was found of full bed rest during the first 6 days after mTBI and, following a return to full activity, gradually from day 7 to day 11 after the injury, compared to a control group of patients with mTBI who were restricted to short bed time rest during the day while being fully mobile from the first day after the injury (137).

There is no systematic follow-up after mTBI in Sweden, which is why patients with persisting symptoms are often "non-systematically referred to various medical specialties with varying competency" (26). A large prospective observational study of 1151 patients with mTBI recruited from ED showed that, in a period of six months, almost half of patients visited a neurologist, and 10% consulted a psychiatrist/psychologist at the outpatient clinic (13).

There are few studies of pharmacological treatments targeting comorbidities after mTBI such as anxiety and depression. Usually, serotonin re-uptake inhibitors (SSRI) are the treatment of choice. Treatment with SSRI has shown an improvement in mood, psychological distress and cognition, in addition to treating depression and anxiety after mTBI (138, 139).

2 AIMS

The overall aim of the thesis was to evaluate the effect of an early intervention in patients at risk for persisting problems after mild traumatic brain injury and to explore potentially treatable factors.

Specific aims were:

- To compare the effect of an early individualized educational follow-up visit offered to patients with many symptoms early after mTBI with the effect of standard care regarding symptom load, activity, participation, quality of life and sickness absence at three months after mTBI (Studies I and II).
- To verify the hypothesis based on previous findings that patients reporting no or few symptoms early after mTBI, have a good outcome, and thus have low risk for persisting disability and no need for routine follow-up (Studies I and II).
- To explore the occurrence and course of visuomotor disturbance by use of objective measures after mTBI, orthopedic injuries and in non-injured controls, and whether objectively demonstrated disturbances correlate with self-reported visual symptoms after mTBI (Study III).
- To explore whether self-rated fatigue is more pronounced in patients with mTBI than in controls, whether self-rated fatigue is associated with cognitive fatigability, and how fatigue correlates with visual functions and attention (Study IV).

3 METHODS

3.1 STUDY PROTOCOL

Studies I and II

Data collection

Eligible study participants received written information about mTBI along with information about the study from the study coordinators or from personnel at the ED. Study coordinators informed the staff of the ED at all participating hospitals on several occasions about the study and the recruitment procedure. Informed consent from the patients was obtained on their discharge from the ED or at the earliest convenience after discharge.

The written information about mTBI included a description of common symptoms and the natural course of recovery. The vast majority of the study population was discharged home from the ED in accordance with then current clinical guidelines in Sweden regarding mTBI. Some study participants were observed in the ED or on a ward for varying time periods but data regarding this were not systematically collected.

The following clinical data were recorded at the ED: mechanism of the injury, duration of loss of consciousness and/or PTA. A computer tomography scan (CT-scan) was performed if judged to be clinically necessary.

Studies I and II are based on the randomized controlled intervention study that was designed in agreement with criteria of Consolidated Standards of Reporting Trials (CONSORT) (140).

Randomization procedure

Ten days after the injury, all patients included reported current symptoms by completing the Rivermead Post Concussion Symptoms Questionnaire (RPQ) (141). Those patients who reported three or more symptoms at the severity levels mild, moderate or severe, i.e. scores 2-4 on the RPQ, were identified as patients with a high risk for persisting problems. 97 patients fulfilling the high-risk criterion were randomized to either to an early intervention visit (EIV) or treatment as usual (TAU). Randomization was centralized and performed by the research coordinator according to an independently generated random allocation sequence in blocks of four. Physicians, specialists in rehabilitation medicine, conducting the intervention were blinded to the randomization procedure.

48 patients were randomized to the EIV group, and 49 patients were randomized to the TAU group. Seventy-six patients that reported no or up to 2 symptoms on RPQ (score 0-2) at 10 days post-injury did not fulfill the symptoms criteria for randomization and were defined as low risk patients.

Blinding

The data collector (GM) and statistician were blinded to group affiliation.

Intervention

At 14-21 days after the injury, the physician, a specialist in rehabilitation medicine, provided all patients in the intervention group with a structured early intervention. Interventions at different study sites were administered by the rigorous protocol.

The early educational intervention visit included:

- A detailed interview about current symptoms and performance in everyday activities, about psychosocial circumstances and occupation, about prior and on-going other somatic and psychiatric disorders and treatments;

- Clinical screening for depression and anxiety including using the Hospital Anxiety and Depression Scale (HADS) (142);

- A thorough standard medical examination including neurological examination;

- Information about symptoms and the natural course of recovery after mTBI; reassurance about the good outcome; recommendations about a gradual return to usual everyday activities

and strategies if symptoms persist. Information provided during the early intervention was in addition to the information about the study and about mTBI received at discharge.

- Interventions for identified problems related to the mTBI or to comorbidities were provided as needed, such as prescription of drugs for pain, anxiety or depression or referral to other specialists or teams.

Treatment as usual (TAU)

Treatment as usual could comprise a contact with health care providers according to local routines, for example, visit to a general practitioner, but no routine follow–up was planned in this study. Standardized written information at discharge from the ED or hospital about symptoms and outcome after mTBI was provided to all patients in the study and thus also a part of the treatment as usual.

Baseline assessments

At the baseline, 10 days after mTBI, all patients included reported symptoms in the RPQ; limitations in activity and restrictions in participation were reported in the Occupation Gaps Questionnaire (OGQ) (143).

Outcome assessments

At follow-up 3 months after mTBI, patients reported symptoms on the RPQ and HADS (Study I). Limitations in activity and restrictions in participation at follow-up were reported on the Rivermead Head Injury Follow-Up Questionnaire (RHFUQ) (144) and on the OGQ, and health-related quality of life was reported on the Short-Form 36 (SF-36) (145, 146) (Study II). Since the OGQ was completed twice, 10 days and 3 months after the injury, changes in perceived gaps could be analyzed.

Data on sick leave and disability pension 6 months before mTBI and 12 months after the injury were collected from the Swedish Social Insurance Agency (Study II). At follow-up, all patients were asked to report any contact with healthcare providers.

Studies III and IV

Studies III and IV are parts of an exploratory prospective observational study that was undertaken between January 2015 and January 2016.

Inclusion procedure

The study coordinators checked the medical records daily at the ED. Patients with mTBI and minor orthopedic trauma who fulfilled inclusion and exclusion criteria were approached at ED or, if discharged, were contacted by phone within 1-3 days after the injury. All study participants received written information about the study. At follow-up, some of the patients were reminded about the follow-up by phone or email.

Data collection

Injury-related information was collected from hospital records, including injury severity characteristics such as GCS on arrival at the ED, loss of consciousness (LOC) and duration of the post-traumatic amnesia (PTA), mechanism of the mTBI, results of the imaging with computer tomography of the brain. Demographic characteristics including education, employment status and on-going studies and medical history were collected by interview with all study participants at the baseline examination.

Initial planning of two visual and neuropsychological assessments at 7-10 days after the injury and at follow-up, 75-100 days after the injury, was adjusted in order to increase participation and minimize dropouts. The median time between injury and baseline visual assessment was 7 days (ranging from 4 to 13 days) for patients with mTBI, and 8 days, (range 7-12 days) for orthopedic controls. The median time between injury and follow-up visual assessment was 103 days (range 81-232) for patients with mTBI, and 108.5 days (range 87-322) for orthopedic controls. Neuropsychological assessment, visual examination and structural and resting state functional magnetic resonance imaging (MRI) were performed at different times on the same day or at adjacent days.

No statistically significant difference was found between patients with mTBI and the orthopedic control group regarding time between the injury and two assessments, at baseline and at follow-up.

The participants of the study were offered a small gift token.

3.2 POWER CALCULATION

Studies I and II

Power calculation was based on a previous study on patients with mTBI with treatment as usual (7). No statistically significant change over time in symptoms intensity, i.e. the sum of symptoms according to RPQ, was found in a high-risk group (mean at day 7 = 27.2, SD = 16.4 vs. mean at 3 months = 27.1, SD = 14.6). Power calculation in this study, accordingly, was based on an expected 50% decrease in symptom intensity of 13.5 points (SD = 15) in the intervention group, and no change in the control group with a power of 85% and a significance level of 5%. The expected difference in change of symptom intensity was equal to an effect size of 0.90 to meet these conditions, 24 patients were required in each group. With an expected attrition rate of 25%, 32 patients had to be included in each group.

Studies III and IV

A power of the study was calculated based on an incidence of 70% in the mTBI group in the previous studies on visual disturbances (71-73) and 10% in the control group (74-76). 10 persons per group were needed in order to detect visual disturbances with 80% power at alpha 0.05. To compensate the calculated attrition rate of 30%, 15 persons were enrolled in each group.

3.3 ETHICS APPROVAL

Studies I and II

The regional ethical review board in Stockholm approved the study, diary number 2007/299/1. The study adhered to the tenets of the Helsinki Declaration. All study patients received written information about the study and gave their written informed consent.

Studies III and IV

Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1. The study adhered to the tenets of the Helsinki Declaration. All study participants received written information about the study and gave their written informed consent.

3.4 SUBJECTS

Studies I and II

Patients with mild head injury and no trauma to other body parts, arriving at the ED no longer than 24 hours after the injury were recruited prospectively to the study from seven regional and county hospitals in Sweden from March 2008 until September 2009.

One hundred and seventy-three patients aged 15-70 were recruited. One patient was diagnosed with a brain tumor later and was, therefore, excluded from the study. One patient was 76 years and was included due to a protocol violation.

Inclusion criteria: closed head trauma with loss of consciousness of less than 30 minutes and /or post-traumatic amnesia (PTA) less than 1hour, GCS 14-15 at the arrival to the ED.

Exclusion criteria were as follows: 1) need for neurosurgery or intensive care, 2) other significant physical injury requiring surgery; 3) any significant somatic or psychiatric disease of a severity likely to impact activities of everyday living; 4) a history of an mTBI that required medical attention during the last 5 years; 5) previous moderate or severe traumatic brain injury; and insufficient knowledge of the Swedish language.

Studies III and IV

Eligible were fifteen consecutive patients presenting to the ED of the Danderyd Hospital, Stockholm, Sweden due to mTBI of such extent that they required an acute CT-scan.

All patients with mTBI met diagnostic criteria according to guidelines of the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (ACRM) (18) and according to the conceptual mTBI definition provided by WHO Collaborating Center of Neurotrauma Task Force on mTBI (17): mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) One or more of the following: confusion or disorientation, loss of consciousness (LOC) for 30 minutes or less, post-traumatic amnesia (PTA) for less than 24

hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS) (2) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. The manifestations of mTBI must not be due to alcohol, drugs, and medications, caused by other injuries or treatment for other injuries, caused by other problems (e.g. psychological trauma, a language barrier or coexisting medical conditions), or by penetrating craniocerebral injury.

Patients were excluded if the duration of loss of consciousness was uncertain (e.g. in combination with alcohol intoxication), if they had contraindications to MRI, any head injury in the previous year requiring medical attention, progressive neurological disorder or any other injury/illness with a short expected survival, need for help in daily living before the current injury, severe visual impairment or manifest strabismus, or were non-Swedish speaking.

Two control groups were included in the study. The first was an orthopedic control group consisting of 15 patients with minor trauma to hand, arm, foot or leg without need of surgical intervention. Inclusion of orthopedic controls was non-systematically intermittent during the same time period as the patients with mTBI. The second control group included staff from the Department of Rehabilitation Medicine, their friends and family members. All study participants were 18-40 years of age.

3.5 NON-PARTICIPANTS

Studies I and II

Seventy-six eligible patients who received study information did not consent to participation in the study. These patients were younger than those who agreed to participate (mean age 29.6 years vs. 39.4 years, $p < 0.001$) and more often men (66% vs. 45%, $p = 0.003$).

Studies III and IV

Ninety-nine patients declined participation in the study: 17 patients with mTBI and 82 patients with minor orthopedic trauma. Most of those who declined were men (88% of patients with mTBI and 64% of orthopedic trauma patients). There was no statistically significant difference regarding age between participating and non-participating subjects. In most cases, the reasons for non-participation were a lack of time and engagement, inconvenience regarding the assessment time frame.

3.6 STATISTICAL ANALYSIS

Studies I and II

All variables were analyzed with descriptive statistics such as mean, standard deviation, 95% Confidence Interval (CI) or median and interquartile range.

Analysis of variance for repeated measures (ANOVA) was used to report mean RPQ scores, and efficacy was expressed as the interaction between the groups and time. Analysis of data

revealed positively skewed distributions of symptom intensity for each of the RPQ symptom ratings. A change score was calculated and then compared between the groups regarding amelioration rate. Non-parametric tests, such as, Kruskal-Wallis (three groups) and Mann-Whitney U (two groups) were used to analyze efficacy, i.e. differences between the groups in change of separate symptom intensity from baseline to follow-up.

Results of SF-36 were presented as median and IQR, since it is an ordinal scale; however, mean and 95% confidence intervals are often presented and are, therefore, also included. In order to explore associations with outcome, univariate binary logistic regression analysis was performed.

Data were analyzed with SPSS version 20. The significance level was $p < 0.05$ (two-tailed) in all comparisons.

Studies III and IV

Oculomotor measures (accommodation, convergence, fusional vergence and saccades) were analyzed with parametric statistics. Interactions between the groups (between-subject factor) and within the group (within-subject factor, baseline to follow-up) were analyzed with two-way analysis of variance for repeated measures. Post-hoc analysis with Holm-Bonferroni adjustment for multiple comparisons was performed. Fischer's exact test was applied for analysis of the categorical data (study III). Dunnet's post-hoc test was used to control for multiplicity (IV). Ordinal data from questionnaires were analyzed with non-parametric statistics: the Kruskal-Wallis test (three groups), Mann-Whitney U test (two groups, post-hoc analysis), Wilcoxon Signed-ranks test and Spearman's rank correlation test.

Data were analyzed using SPSS version 23. Two-tailed p values were used with a critical significance level of $p < 0.05$.

3.7 OUTCOME MEASURES

3.7.1 Evaluation of symptoms, activity and participation, and health related quality of life

Rivermead Post Concussion Symptoms Questionnaire (RPQ)

The RPQ is a self-rated Likert scale type questionnaire for measuring symptoms that are often reported after mTBI. This scale evaluates 16 symptoms: headaches, dizziness, nausea/vomiting, fatigue, noise sensitivity, light sensitivity, irritability, feeling depressed, sleep disturbance, feeling frustrated, restlessness, forgetfulness, poor concentration, taking longer to think, blurred vision, double vision. Patients are asked to rate symptoms compared to pre-injury status on a scale of 0-4, where 0 means "not a problem", 1 – "no more of a problem", 2 - "mild", 3 – "moderate", and 4 – "severe problems". The mean score of the 16 items/symptoms, i.e. symptom load was calculated as the primary outcome measure (study I).

RPQ has shown good test-retest reliability 7-10 days and 6 months after mTBI (141). Rasch analysis (a mathematical model, which determines whether items from the scale in the questionnaire fit into this model) of the RPQ (147) has shown that RPQ is not a unidimensional instrument. RPQ questions were separated into two symptom scales RPQ-13 and RPQ-3, and each of these scales have shown unidimensionality. Structural analysis of the RPQ (148) showed that this questionnaire has a three factor, not a one factor structure, including somatic, cognitive and emotional factors, but that there is a high degree of co-variation between factors. Putting somatic and emotional factors together into a two-factor model showed goodness–of–fit to the data.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a short self-reported questionnaire, which is used to assess anxiety and depression levels (142). This questionnaire consists of the two subscales, the HADS –anxiety and HADS-depression scale with 7 items each. Patients are asked to rate their symptoms during the past week. Each item has a 4-point scale from 0 (not at all) to 3 (very often) with a maximum score of 21 for each of two scales. In each domain scores of 0-7 are categorized as normal, 11-14 – as moderate, and 15-21 as severe.

HADS showed good sensitivity and specificity at a cut-off score over 8 for each of the two scales (149).

Occupational Gaps Questionnaire (OGQ)

The OGQ was developed so as to measure the individuals' perceived participation in activities of everyday life, in social and work-related activities. The ability to perform everyday activities might be affected because of the disease or illness. Individuals might perceive difficulties in everyday occupations causing a gap between what the individual wants to do and what they actually do. Consequently, the gap might appear between what the individual does but does not want to do. The presence of occupational gaps in OGQ is examined in 28 activities, consisting of 8 instrumental activities of daily living, 6 social activities, 10 leisure activities and 4 work-related activities. This questionnaire has been validated in different medical conditions such as stroke, subarachnoid hemorrhage and traumatic brain injury inclusive mTBI (143).

Rivermead Head Injury Follow Up Questionnaire (RHFUQ)

The RHFUQ measures self-rated head injury-related changes in routine domestic activities and in participation in work and social life, and interactions with family and friends (144). This questionnaire was developed in order to assess activity and participation after mild to moderate brain injury. RHFUQ includes ten questions with ratings on a Likert scale from 0 to 4: 0 – "no change", 1 – "no change, but more difficult", 2 – "mild change", 3 – "moderate change", 4 – "very marked change". Ratings 2-4, "mild change" to "very marked change" were aggregated to a single score "Problems". Summarizing scores for all ten items gives a total score with a maximum of 40.

According to previous studies (61, 77), we have dichotomized summary scoring of injury-related every day activities on RHFUQ as follows: a total sum score less than 8 meaning a "good" outcome and a sum score of 8 or higher meaning an "unfavorable" outcome.

Short-Form Health Questionnaire (SF-36)

The SF-36 is a short form survey of health-related quality of life (145). It consists of 36 questions and assess eight health scales/domains: 1) limitations in physical activities due to health problems; 2) limitations in social activities due to physical or emotional problems; 3) limitations in usual role activities due to physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Patients are asked to rate their health over the past 4 weeks. One of the 36 questions asks about health over the past year and is not included in the eight health domains. The SF-36 scales are summarized in two distinct summary scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS). In order to evaluate the results of the SF-36, each scale is transformed into a 0-100 scale where a lower score means greater disability, and higher score means less disability.

The SF-36 is a generic questionnaire. It targets general and specific populations, and is used to estimate the impact of different treatments on general health. In 1995, Sullivan et al. published an article exploring the reliability and construct validity of the Swedish version of the SF-36 in a large Swedish general population (146). In all, 8 930 respondents participated in seven general population surveys (age interval 15-93 years, mean age 42.6 years). The Swedish study showed a good internal validity and reliability across different age and socio-demographic groups (146).

3.7.2 Vision

Visual examination

Experienced licensed optometrists performed visual examinations of all study participants in agreement with a standard clinical optometric procedure. It included assessment of monocular and binocular visual acuity at far and at near, refractive error, near point of accommodation, accommodation facility, near point of convergence, fusional vergence and non-strabismic eye-turn, heterophoria. Visual dysfunctions were diagnosed according to established diagnostic criteria (150). One of the oculomotor –based visual impairments is convergence insufficiency (CI). The point, where eyes achieve maximum convergence, is called the near point of convergence (NPC). Convergence insufficiency was diagnosed when NPC was at a distance greater than 6 cm plus at least one of the following: reduced PFV at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance (150). Positive fusional vergence is an ability to align the eyes despite the increasing vergence demands, as it is in assessment with a prism bar. The patient was instructed to try as hard as possible to maintain single vision while the examiner was gradually increasing the strength of the prism, and then to report when double vision

appeared. A similar procedure was used in the testing of NPC, which was measured with an RAF-ruler. Expected accommodative amplitude was calculated according to the Hofstetter formula (18.5-1/3 age). Accommodative insufficiency was diagnosed if the accommodative amplitude was below the minimum expected according to the Hofstetter formula (15-1/4 age) (150).

Saccades

Saccadic eye movements were recorded (spatial res 0.15 degrees; temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The participant was seated so that his head was positioned at a distance of 60 cm in front of the eye tracker stimulus screen. Three saccadic test paradigms were used: (1) stimuli-induced pro-saccades; 2) anti-saccades; and (3) self-paced saccades. The stimuli consisted of a dot with a diameter of 5 mm (0.5 degrees). In the prosaccade paradigm the participant fixated on a centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or right of the cross. The performance was characterized with mean latency and positional gain. In the anti-saccade paradigm, the participant viewed a centered cross and was instructed to inhibit their reflexive gaze at a dot presented 8 degrees to the left or right of the center, and, instead, rapidly look in the opposite, mirror-wise location of the presenting dot. Antisaccades were characterized with the latency of correctly performed saccades and proportion of erroneous saccades. In the self-paced saccade paradigm, two dots were simultaneously presented for 30 seconds at 8 degrees to the left and right of center. The participant was instructed to move the gaze rapidly, as many times as possible, between the dots. The performance was characterized with the number of saccades performed in 30 seconds and the mean intersaccadic interval.

Visual symptoms

Visual symptoms were assessed at the baseline and at follow-up using the Convergence Insufficiency Symptom Survey (CISS) (151, 152). The CISS assesses near work-related visual symptoms (151) and includes assessment of direct symptoms, such as blurred vision and double vision, as well as indirect symptoms (difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort). The survey includes 15 questions with ratings from 0 ‘never’ to 4 ‘always’ for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21. This value gives good sensitivity (97.8%) and specificity (87%) in otherwise healthy young adults who have presented to optometrists with visual symptoms (152).

3.7.3 Fatigue and cognition

Fatigue Severity Scale (FSS)

General, or trait fatigue, was measured with FSS (98). The FSS is a questionnaire, which includes 9 questions on a 7-point Likert scale: from 1 - “Strongly disagree” to 7 - “Strongly

agree". The final score is an average of all 9 questions scores. A higher score means a higher level of fatigue. The cut-off score of 4 and above indicates perceived present fatigue.

Cognitive tests

All patients were assessed with four neuropsychological tests: The Digit Symbol Substitution Test (153), The WAIS-III Digit Span test, The Ruff 2 & 7 Selective Attention Test (154), The Swedish Lexical Decision Test.

The Digit Symbol Substitution Test (DSST) (153) is a well-established psychometric test paradigm used for measuring psychomotor processing speed. Participants were asked to write down one of the 9 corresponding symbols paired to a digit, as quickly as possible. This test requires a continuous performance during 120 seconds. The test score is a number of correct matches between digits and symbols. Before starting this test, participants were allowed to perform one session with 7 digits to practice, according to the test manual. Learning capacity can influence psychomotor speed; therefore, the participants were asked to write down the correct symbol under each digit twice after four completed rows, hence measuring incidental memory, i.e. memory for information which was secondary to the task and which participants were not instructed to remember (155).

Cognitive fatigability (DSST-f) was calculated in this study by subtracting the score for the first half of the test (60 first seconds) from that from the last part of the test (60 last seconds), where the negative score indicated reduced performance on the test. Generally, it is expected that due to learning, the number of digits would increase in the second part of the test. Therefore, a non-increasing test score could indicate fatigability (155).

The WAIS-III Digit Span test (DS) was used to measure verbal attention span with a forward repetition of digits, and verbal working, or short-term, memory with backward repetition of digits, that requires executive function (153, 156). Sum scores for forward and backward repetition are presented separately.

The Ruff 2 & 7 Selective Attention Test (154) measures visual automatic detection speed (ADS) and automatic detection accuracy (ADA), controlled search speed (CSS) and controlled search accuracy (CSA). The participants had to mark targets, numbered 2 and 7, that were embedded among the letters (ADS) or among the other numbers (CSS). The test consists of a randomly ordered 10 sections measuring ADS and 10 sections measuring CSS. The test, with total time of 5 minutes, was administered as a continuous performance test according to the manual (154). Correct markings of targets and errors were counted after each section. Accuracy scores were calculated as the number of targets identified in relation to all possible targets. Higher scores indicated better performance. One section of ADS and one section of CSS were allowed for practice before the test.

The Swedish Lexical Decision Test (SLDT) test measures the estimated premorbid cognitive global function (premorbid intelligence) based on word knowledge (157). Participants were

presented with a list of words, and they had to decide whether the word was a real or fictional.

3.7.4 Sickness absence

Sickness absence is an absence from the work that is attributed to sickness by the employee himself or by their physician. Sickness absence includes sickness benefits such as sick leave and disability pension that can be for full-time or part-time. People on part-time sick leave or disability pension can work part time.

Register data from the Swedish Social Insurance Agency were collected on all study patients regarding compensated sick leave days for the time period 6 months before the mTBI and 12 months after the injury. Data on disability pensions were also included if applicable. Data on one of the patients were not included due to an administrative error.

Register data from the Social Insurance Agency in Sweden include sick leave diagnoses codes according to International Classification of Diseases, 10th Revision (ICD-10) (47). The codes are presented at a three-digits level. However, the closest code to diagnosis of mTBI in ICD-10 is S06.0 “Concussion” or “Commotio cerebri” that includes four digits and is, therefore, not available in the Social Insurance Agency register. In this study, in order to define sickness absence due to mTBI, the code S06 “Intracranial injury” was used. Data on two study patients with diagnosis codes describing medical conditions similar to that of S06.0 were included; one patient had a diagnosis F072 “Postconcussional syndrome”, another patient had the diagnosis S099 “Other and unspecified head injuries”.

4 RESULTS

4.1 STUDIES I AND II

A flow-chart of the study is shown in Figure 1.

In both randomized groups, 83% of study patients completed the study. There were statistically significantly more falls as the injury mechanism in EIV group compare to TAU group ($\chi 2 = 6.27$, $p = 0.012$). No other differences between randomized groups were found regarding sociodemographic or clinical characteristics.

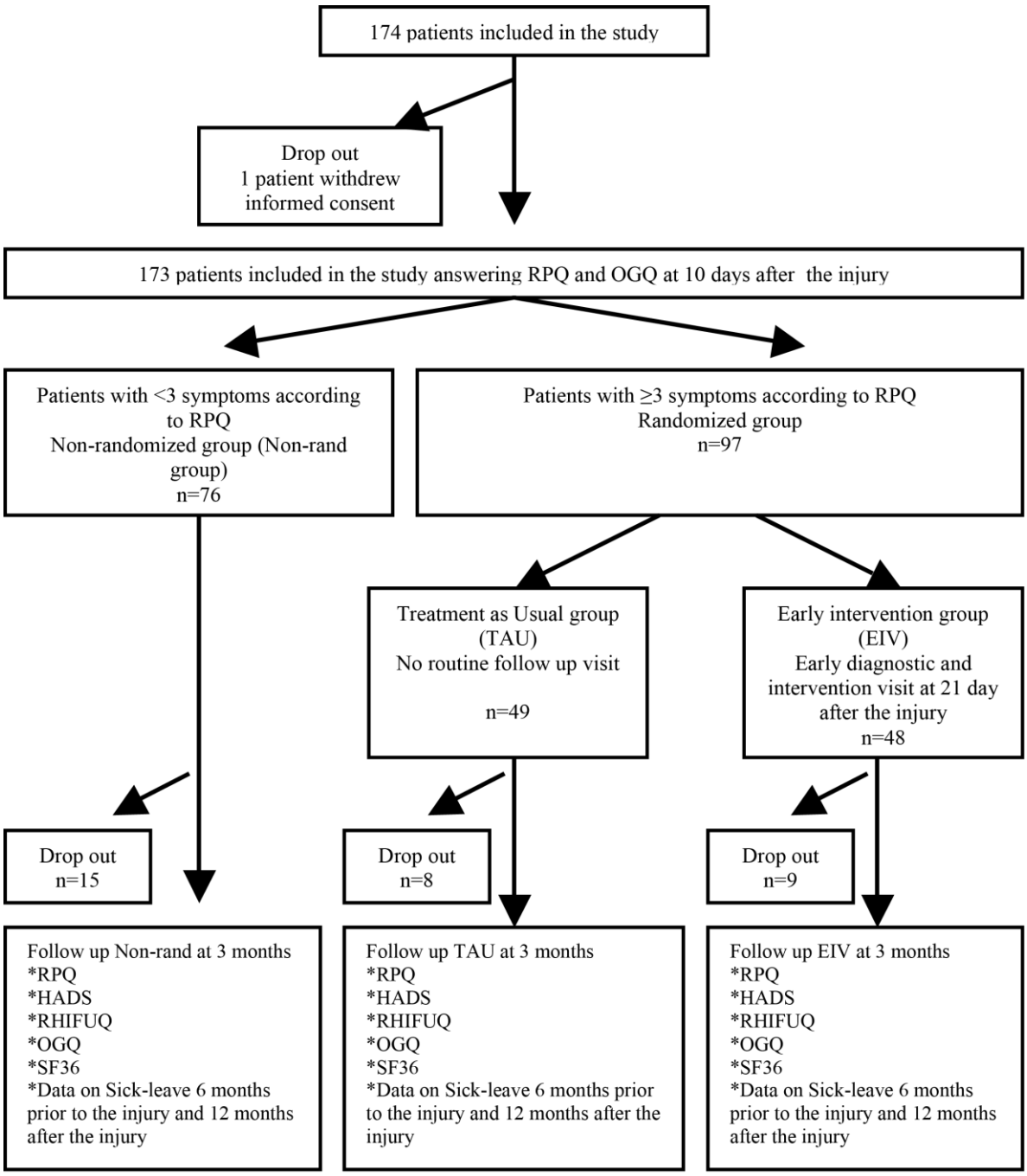

Figure 1. Flow-chart of the studies I and II.

The CT-scan of the brain showed the following results: in the EIV group one patient had both a skull fracture and small hemorrhage, and one patient had a skull fracture; in the TAU group, one patient had a small hemorrhage and three patients had skull fractures; in the non-randomized group, 2 patients had small hemorrhages and 3 patients had skull fractures.

Sociodemographic characteristics of study patients are presented in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients randomized to treatment as usual (n = 49) or to an early intervention (n = 48), and non-randomized patients (n = 76).

Characteristic		Low risk	High risk	
		Non-randomized	Treatment as usual	Intervention
Age	Mean	39.6	37.5	41.0
	Range	15 – 76	15 - 68	15 - 69
Men	n (%)	40 (53)	23 (47)	15 (31)
Women	n (%)	36 (47)	26 (53)	33 (69)
Type of accident,	n (%)			
Fall		33 (43)	14 (30)	25 (53)
Car accident		3 (4)	1 (2)	2 (4)
Bicycle accident		11 (15)	7 (15)	5 (11)
Horse riding		5 (7)	9 (19)	8 (17)
Sport		16 (21)	9 (19)	2 (4)
Assault		3 (4)	3 (6)	3 (6)
Other		5 (7)	4 (9)	2 (4)
Positive test for alcohol in blood n (%)		13 (24)	3 (9)	4 (12)
GCS	Range	14 – 15	14 - 15	14 - 15

4.1.1 Symptoms reporting on RPQ in high and low risk groups

No statistically significant difference regarding the symptoms between the two high risk groups, EIV and TAU were found at follow-up [$t(78) = 1.62$, $p = 0.11$]. Symptom load was statistically significantly higher in the EIV group compared to the TAU group at the baseline [$t(95) = 2.24$, $p = 0.027$]. Symptom load decreased statistically significantly in both randomized groups [$F(1, 78) = 58.28$, $p < 0.001$], but no statistically significant difference was found between the two randomized groups in the amelioration rate [$F(1, 78) < 1.00$, $p = 0.790$] from baseline to follow-up.

The intensity of each of the RPQ symptoms was analyzed at group level as is shown in Figure 2. The symptoms “Headache” and “Fatigue” had the highest intensity at the baseline in both randomized groups, and in the TAU group at follow-up. In the EIV group most prominent symptoms at follow-up were “Fatigue” and “Poor concentration”.

In the non-randomized group symptom load was lower compared to the randomized groups, and there was no statistically significant difference in the change of each of the symptoms over time.

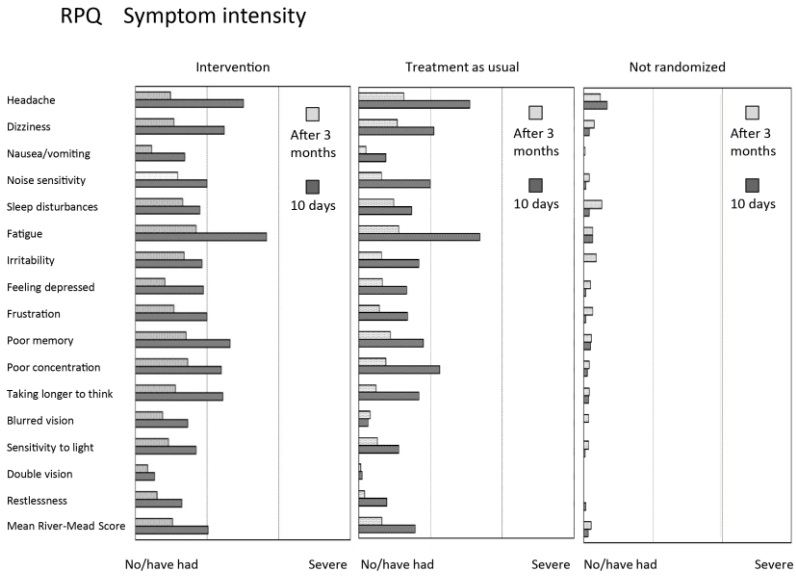

Figure 2. Mean symptom intensity scores at baseline and at 3 months post-injury in (a) patients randomized to early intervention, (b) patients randomized to treatment-as-usual and (c) non-randomized, low risk patients.

Anxiety and depression

Three patients in the EIV group had treatment for anxiety and depression disorders with psychotherapy or serotonin reuptake inhibitors prior to mTBI, as revealed at the intervention visit. One patient, who was diagnosed with depression symptoms by clinical examination and HADS scores during the intervention visit, declined the recommended anti-depressive treatment. These four patients' psychiatric morbidity did not affect their everyday life activities before the injury, and they were included in the study.'

4.1.2 Outcome regarding activity and participation

RHFUQ

Analysis of the activity and participation items in RHFUQ showed that a large proportion of the patients in non-randomized group reported having no change in most of the items compared to before the injury. Statistically significant difference was found regarding reported changes in everyday and social activities in RHFUQ between two randomized and non-randomized groups ($df = 2$, $p < 0.001$)(Kruskal-Wallis test). Post-hoc analysis with the Mann-Whitney U test showed a significant difference between the EIV group and non-randomized group ($U = 705.0$, $p < 0.001$), and between the TAU and non-randomized group ($U = 730.5$, $p < 0.001$) (Mann-Whitney U test). No statistically significant difference was found between the two randomized groups. Patients in all three groups reported the highest rating in the item "Work more tiring".

OGQ

A statistically significant difference between the randomized and non-randomized groups was found (df = 2, p < 0.001) (Kruskal-Wallis test) regarding the reported occupational gaps in the OGQ questionnaire at the baseline on day 10 after the injury (Figure 3). Each randomized group differed statistically significantly compared to the non-randomized group: EIV versus non-randomized group (U = 379.5, p < 0.001), and TAU versus non-randomized group (U = 341.5, p < 0.001). There was no significant difference at the baseline between randomized groups regarding occupational gaps (U = 581.5, p = 0.88) (Mann-Whitney U test). No difference regarding occupational gaps was found between any of the groups at the follow-up. The number of occupational gaps decreased in all three groups from baseline to follow-up (Figure 3). A statistically significant decline in occupational gaps was found between baseline and follow-up in the EIV group (z = -1.117, p < 0.001) and in the TAU group (z = -4.26, p = <0.001) (Wilcoxon Signed-ranks test) with no significant difference in non-randomized group. The non-randomized group had a low number of occupational gaps in all items at both time-points. There was a statistically significant difference in change over time in all three groups regarding reported occupational gaps (df = 2, p < 0.001) (Kruskal-Wallis test) with a significant difference between the EIV and non-randomized group (U = 627.0, p < 0.001) and between the TAU and non-randomized group (U = 608.0, p < 0.001) with no difference between the two randomized groups (U = 747.5, p < 0.9) (Mann-Whitney U test).

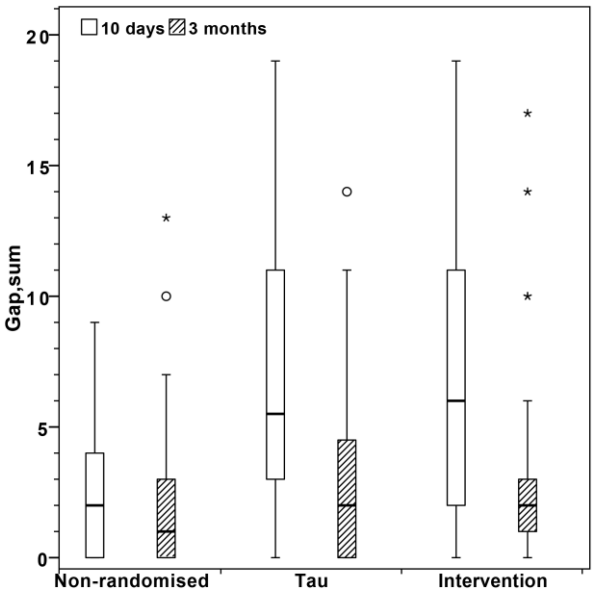

Figure 3. Sum of perceived occupational gaps at 10 days, baseline and at 3 months, follow-up after mTBI in early intervention (EIV), treatment-as usual (TAU) and non-randomized groups.

In both randomized groups, EIV and TAU, the predominant occupational gap “not doing but wanting to do” was reported in social and leisure activities, such as sports, seeing relatives and friends, engaging in societies, clubs and unions. Another type of occupational gap “doing but not wanting to do” was most prevalent in all three groups regarding activities of instrumental ADL such as shopping, cooking, washing clothes, cleaning, performing light maintenance, and managing personal finances both at baseline and at follow-up.

4.1.3 Outcome regarding quality of life

SF-36

Both randomized groups reported a lower quality of life compared to the non-randomized group. There was a significant difference among the three groups regarding SF-36 data in the scales Vitality (df =2, p = 0.01), Mental Health (df = 2, p = 0.001), Bodily Pain (df =2, p = 0.04), (Kruskal-Wallis test). Post-hoc analysis with the Mann-Whitney U test revealed a statistically significant difference between the EIV and non-randomized groups in Vitality (U = 685.5, p < 0.001), Mental Health (U = 808.0, p = 0.005), Bodily Pain (U = 887.0, p = 0.017), Role Physical (U = 973.5, p = 0.038), and between the TAU and non-randomized groups in Vitality (U = 759.0, p = 0.023), General Health (U = 767.5, p = 0.027), Role Emotional (U = 905.5, p = 0.024). Regarding Mental Component Score (MCS) in SF-36, a statistically significant difference was observed between all three groups (df = 2, p = 0.011) (Kruskal-Wallis test), and between the EIV and non-randomized groups (U = 784.0, p = 0.007), and the TAU and non-randomized groups (U = 730, p = 0.028) (Mann-Whitney U test) (Figure 4). No difference was found between the two randomized groups.

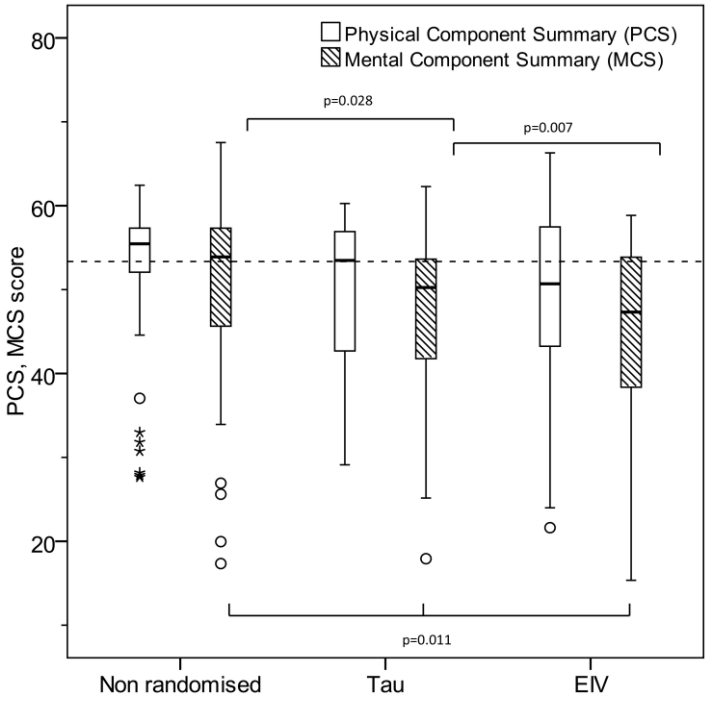

Figure 4. Short-Form 36 (SF-36) summary measures: physical component score and mental component score. TAU: treatment as usual; EIV: early intervention. ° mild outliers, * extreme outliers.

4.1.4 Outcome regarding sickness absence

The majority of the eligible patients (76%, 131 of 172) had no sickness absence compensation between 6 months before and 12 months after mTBI. Totally, thirty patients had sick leave after mTBI. There were 8 patients in EIV group and 6 patients in TAU group who had sick leave due to diagnosis S06 ”Intracranial injury” (Figure 5). Most of the patients with sickness absence after mTBI discontinued their sick leave in less than 3 months.

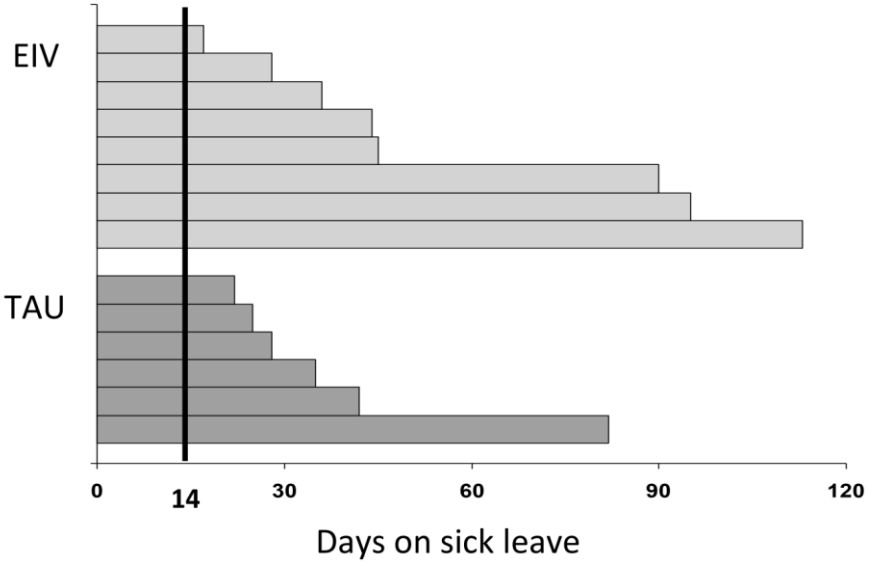

Figure 5. Distribution of the number of sick leave days in the 14 patients with the diagnosis “Intracranial injury”, S06. The number of sick leave days is presented as “gross” days, i.e. regardless of whether sick leave applies only to part of the day.

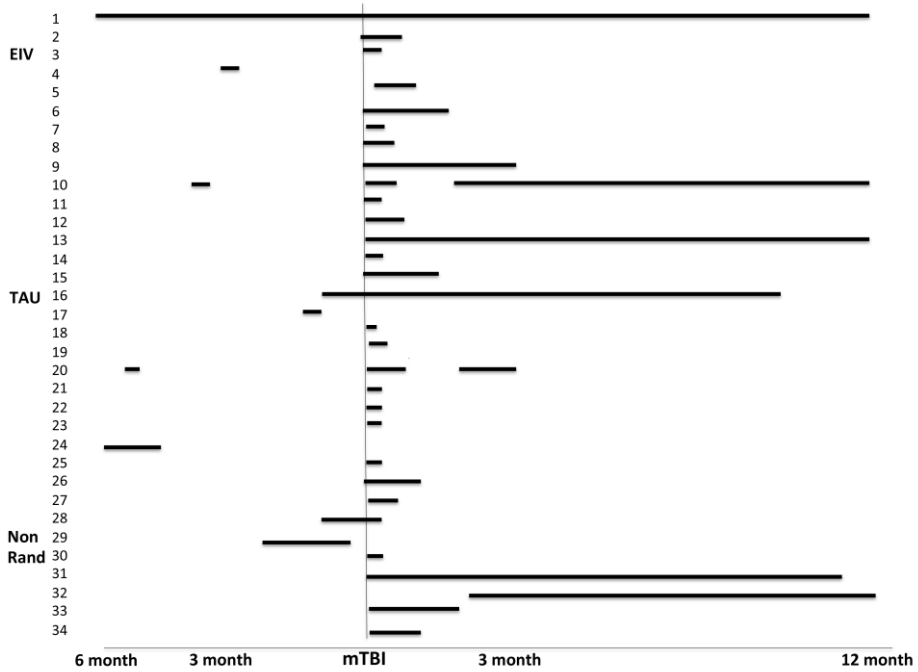

Figure 6. Distribution and duration of all sick leave periods (during the period 6 months before to 12 months after MTBI) among the patients in all three groups.

Eleven patients that were on disability pension during the period 6 months before and 12 months after mTBI had been on disability pension to the same extent both before and after the injury. Four of them had part-time sick leave and disability pension (158). During the period of 6 months before mTBI only 9 patients (5%) had sick leave (longer than 14 days). Few patients, mostly in the EIV group, had longer sick leave periods after mTBI. Patients that had longer periods of sick leave after mTBI did not tend to have more sickness absence before the injury (Figure 6). In the EIV group, one patient had sick leave after mTBI with diagnosis code S06 and then again, after returning to previous activities, had sick leave period with the diagnosis of depression.

4.2 STUDIES III AND IV

Patients were assessed twice after mTBI in studies III and IV, at baseline, also called as sub-acute stage, and at follow-up. CT-scan of the brain showed that two of the patients with mTBI had pathological changes without the need for neurosurgery: one had a small subdural hemorrhage and the other a small subarachnoid hemorrhage. Sociodemographic characteristics are shown in Table 2.

Table 2. Sociodemographic characteristics of patients with mTBI, orthopedic and non-injured controls.

	Patients with mTBI	Orthopedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (%)	14 (93)	N/A	N/A
GCS 14 (%)	1 (7)	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47) Bicycle: 2 (13) Horse riding: 2 (13) Other: 4 (27)	Sports: 9 (60) Other: 6 (40)	

4.2.1 Vision

Visual assessments

Accommodation

Regarding the deviation from expected accommodative amplitude, a significant effect of interaction between groups and test occasions was found in the ANOVA (df=2, F=4.406, p =

0.028). At the baseline, statistically significantly reduced accommodative amplitude (p = 0.001) was found in the mTBI group compared to a non-injured control group, and no significant difference between the mTBI and orthopedic control groups according to post-hoc analysis (Figure 7). No difference was found between all three groups at follow-up. Of all 15 patients with mTBI, 12 had accommodative insufficiency (AI) at the baseline, and 6 out of 13 patients with mTBI still had AI at follow-up compared to 5 out of 12 orthopedic controls and 2 out of 15 non-injured controls, with no changes over time in both control groups. There was no statistically significant difference in accommodative facility within or between the groups or test occasions.

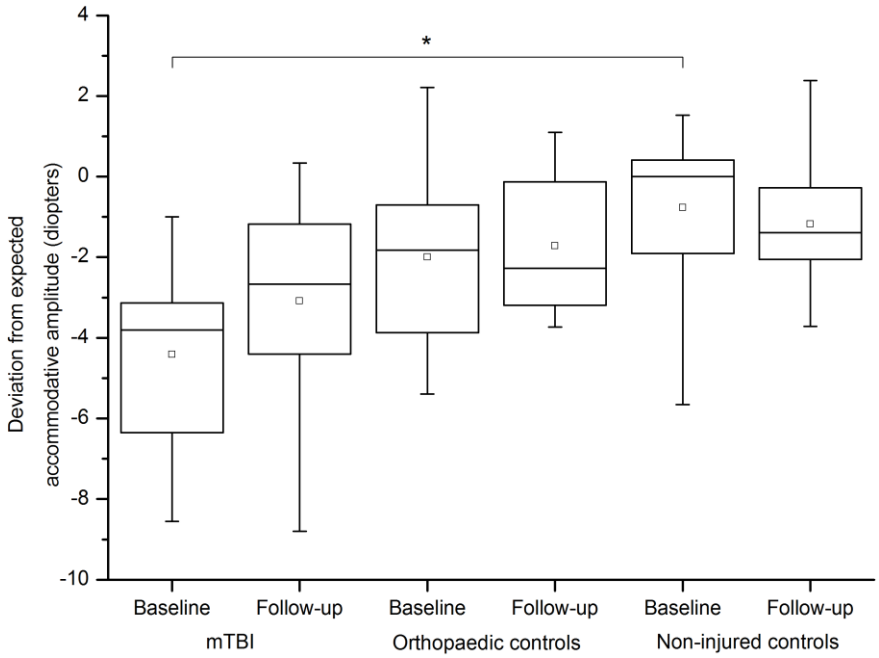

Figure 7. Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartiles. The whiskers indicate minimum and maximum. * Significant difference (p = 0.015).

Convergence

There were no significant differences between the mTBI group and both control groups at either occasion. There was a statistical significant improvement in the mTBI group, as shown with post-hoc analysis, from baseline to follow-up (p = 0.015) (Figure 8). No statistically significant differences were found between or within both control groups.

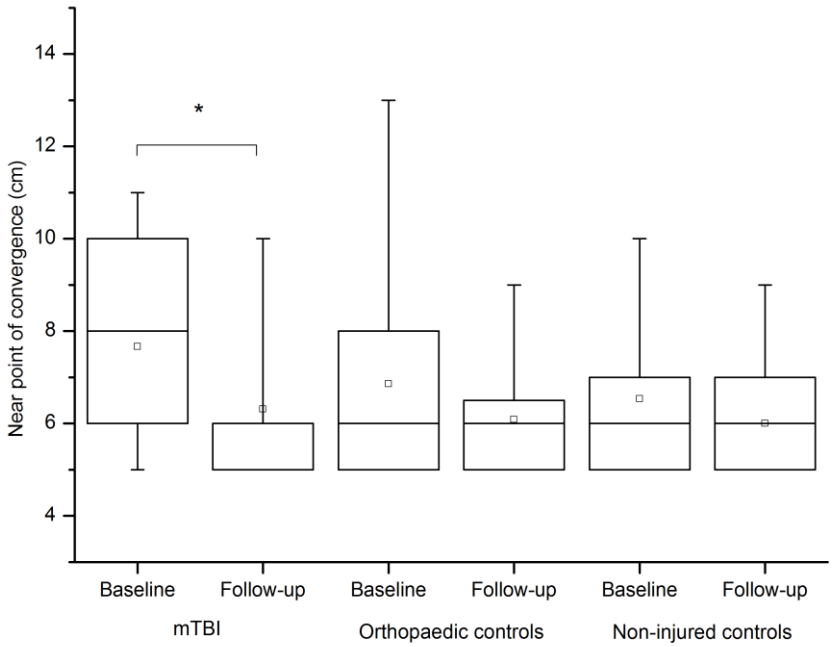

Figure 8. Near point of convergence in the mild traumatic brain injury (mTBI) group at baseline and at follow-up measured in centimeter. The lower the value, the better the convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate minimum and maximum.
* Significant difference (p = 0.015).

Fusional vergence

The ANOVA on fusional vergence did not show any significant differences at the group level at any time point.

Saccade performance

No statistically significant difference in latency was found between groups or test occasions in the prosaccade task (ANOVA). There were no significant differences within or between groups in the self-paced saccade task. Performance of the antisaccade task in all three groups showed no statistically significant differences in latency or proportion of erroneous saccades.

Assessment of visual symptoms

A statistically significant difference in CISS score between the three groups was found at the baseline (df = 2, p = 0.003) (Kruskal-Wallis test). Post-hoc analysis revealed that patients with mTBI had more visual symptoms with near work at the baseline compared to both control groups: patients with mTBI versus orthopedic controls (U = 47.5, p = 0.012) and patients with mTBI versus non-injured controls (U = 38.0, p = 0.02) (Mann-Whitney U test). In the mTBI group, the median value of the CISS score decreased from 24 at the baseline to 19 at follow-up without reaching statistical significance (Wilcoxon Signed-ranks test). In the control groups the CISS score was bellow cut-off level at both time points.

Figure 9 illustrates associations between CISS score and AI/CI in all three groups at both time points. According to CISS, nine of twelve patients with mTBI were identified with CI or AI at baseline, and seven patients with mTBI still had CI or AI at follow-up: one with CI and six with AI. Three of these patients score above the cut-off level on CISS. There was no association found between CISS and CI/AI (Fischer's exact test).

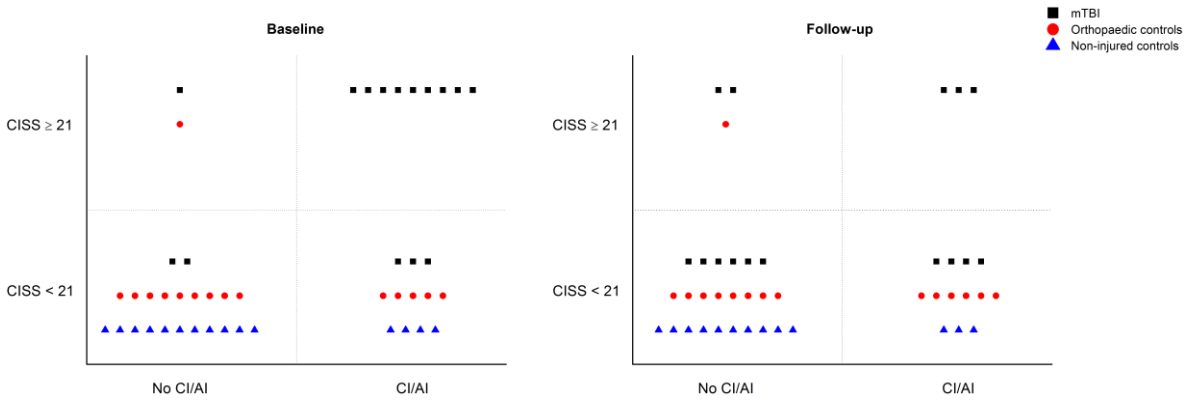

Figure 9. The association between Convergence Insufficiency Symptom Survey (CISS) score and the presence of accommodative insufficiency (AI) or convergence insufficiency (CI) in patients with mild traumatic brain injury (mTBI), orthopedic controls and non-injured controls. The findings at baseline and at follow-up are presented in a two-by-two matrix.

The CISS scores correlated at baseline with reduced PFV measured at near, i.e., the capacity to maintain clear single vision while performing near work. (r = -0.6, p = 0.02) (Figure 10).

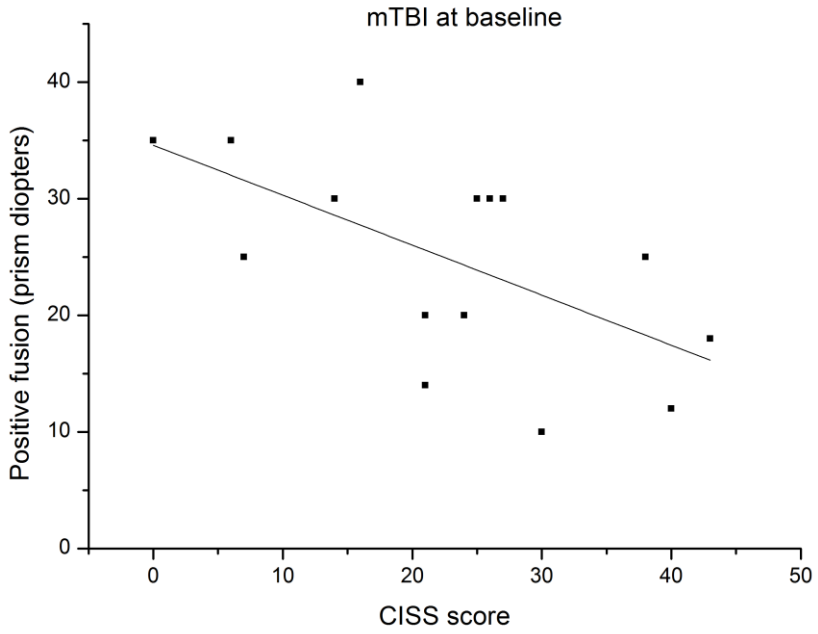

Figure 10. Convergence Insufficiency Symptom Survey (CISS) score versus positive fusional vergence in patients with mild traumatic brain injury (mTBI). Higher positive fusion value corresponds to better function.

Symptoms measured by the RPQ

A statistically significant difference was found among the three groups in the sum of symptoms scores on RPQ at baseline (df = 2, p < 0.01) and at follow-up (df = 2, p = 0.001) (Kruskal-Wallis test). Post-hoc analysis showed a statistically significant difference in the RPQ sum of symptom scores between the mTBI group and the orthopedic control group (U = 40.0, p = 0.002) and between the mTBI group and the non-injured control group (U= 40.0, p = 0.002) at baseline, as well as at follow-up: mTBI versus the orthopedic group (U = 27.0, p = 0.003), mTBI versus the non-injured control group (U = 24.0, p < 0.001) (Mann-Whitney U test). The sum of symptom scores decreased in the mTBI group over time, but the difference did not reach statistical significance (p = 0.092) (Wilcoxon Signed-ranks test).

4.2.2 Fatigue and cognition

The first neuropsychological examination at the sub-acute stage was performed in the mTBI group the median was 6 days after the injury (range 4-12 days) and for the orthopedic controls 8 days (range 2-9 days). The median time for the follow-up neuropsychological examination was 95 days (range 81-225 days) for the patients with mTBI and 108 days (range 87-324 days) for the orthopedic controls. There were no differences in age, gender, length of education or estimated IQ between the two trauma groups, but the non-injured control group had a significantly longer education and a higher estimated full-scale IQ.

Sub-acute stage

There was a statistically significant difference between the three groups for self-rated acquired fatigue, RPQ-f (df = 2, p = .001), and the mTBI group scored significantly higher on acquired fatigue compared to the orthopedic control group (U = 58.5, p = .023) (Fig.11a). The patients with mTBI scored around the cut-off level for trait fatigue (FSS) (Fig.11b). There was also a statistically significant difference regarding trait fatigue (FSS) between the three groups (df = 2, p = .033), but trait fatigue did not differ significantly between the mTBI group and the orthopedic control group (U = 64.5, p = .077) (table 3). When comparing three groups regarding cognitive fatigability (DSST-f), no statistically significant difference was found (F(2,41) = 2.964, p = .063). The post-hoc analysis with the Dunnett test showed that the patients with mTBI had more fatigability compared to the orthopedic controls, mean difference, (2.80, [0.12 – 5.48], p = .039) (Fig. 11c).

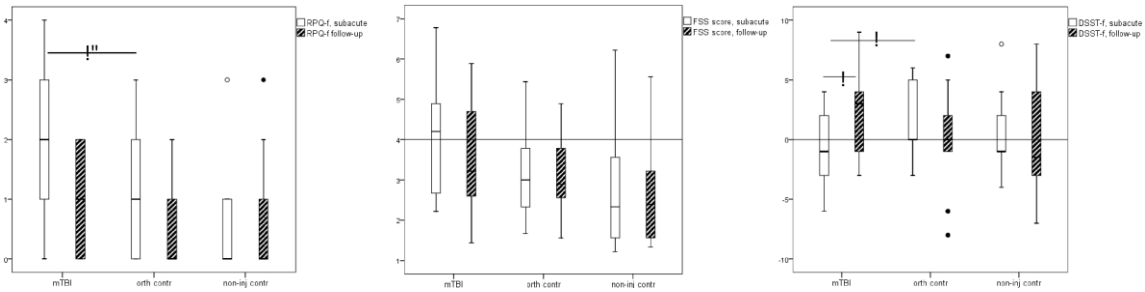

Figure 11 a-c. Acquired fatigue, trait fatigue and cognitive fatigability at sub-acute stage and at follow-up. * p < .05

There was no difference between the three groups regarding anxiety and depression at the sub-acute stage. In the mTBI group, anxiety correlated with trait fatigue (FSS) (r_{mTBI} = .716, p = .006). Depression did not correlate with any of the fatigue measurements.

Visual functions such as convergence, accommodation did not correlate to any of the fatigue measures. Regarding saccade measurements, there were no statistically significant differences between the three groups, except for the variability of prosaccade latency (PSL) (F(2,39) = 3.543, p = .039). Post-hoc analysis with the Dunnet test showed a statistically significant larger variability of prosaccade latency between the mTBI group and the orthopedic control group, mean difference, (-14.55, [-28.62 – -.47], p = .042), but not between the mTBI group and the non-injured control group. In the mTBI group, some of the saccade measures correlated to different fatigue measures. Acquired fatigue (RPQ-f) correlated positively with PSL (r_{mTBI} = .690, p = .006), but not with any of the other saccade measures. That is, the higher the acquired fatigue, the higher the prosaccade latency.

Trait fatigue (FSS) correlated with antisaccade latency (ASL) (r_{mTBI} = .588, p = .035) and also with the variability of ASL (r_{mTBI} = .637, p = .019). That is, the higher the scores of trait fatigue the higher the latency and higher variability in antisaccade presentation. However, there was a high correlation between FSS and anxiety among the patients with mTBI. When partial correlation was performed, the correlation between FSS and antisaccade latency, controlling for anxiety, did not remain significant for any of the groups.

In the mTBI group, acquired fatigue correlated with cognitive fatigability (DSST-f) (r_{mTBI} = -.527, p = .043). That is, the higher the self-rated fatigue the greater the fatigability. Trait fatigue did not correlate with any of the attention measurements in the mTBI group. For the mTBI group, cognitive fatigability (DSST-f) correlated positively with controlled search accuracy (CSA) (r_{mTBI} = .585, p = .022). That is, the more fatigability, the more errors on Ruff 2&7 on the subtask demanding controlled attention functions. No correlations were found between cognitive fatigability and incidental memory, attention span or working memory in any of the groups.

Follow-up

Both acquired fatigue and cognitive fatigability improved from the sub-acute stage for the patients with mTBI to the follow-up. There were no longer significant differences between the mTBI and control groups regarding acquired fatigue, trait fatigue (FSS) or cognitive fatigability. None of the patients with mTBI had severe problems with fatigue at follow-up. However, nearly half of the patients with mTBI had some residual problems with acquired fatigue. Most of the patients with mTBI improved from the sub-acute stage regarding cognitive fatigability. However, three of the patients showed poorer results compared to the sub-acute stage.

5 DISCUSSION

5.1 INTERVENTION FOR PATIENTS AT RISK FOR PERSISTING DISABILITY

The intervention in this study aimed to promote a good outcome in patients who were considered at high risk for prolonged symptoms. However, there was no effect of the intervention on reported symptoms, or on activity and participation three months after the injury.

Previous studies provide sufficient evidence that early information on the usual course and a probable good prognosis is beneficial (14, 129, 159, 160). The written information given to all study patients might be sufficient to promote recovery, without an additive effect of the intervention. Furthermore, we also speculated that assessing and discussing possible comorbidities as a part of the intervention might, instead of reassuring patients of a possible good outcome, have alerted them to possible symptoms. Patients in the intervention group reported more symptoms and had more limitations in activity and participation at follow-up, but this was not a statistically significant.

Another reason that we found no effect of the intervention might have been that criteria for identification of patients at risk for persisting problems were too narrow, for example, they only took into account the number of symptoms, not symptom severity. In this study, the group of patients with an estimated high risk for a poor outcome was defined by those who reported 3 or more symptoms, as it is described in the definition of Postconcussional syndrome in ICD-10 (47), a risk criterion also used in other studies (7). However, even when analyses were performed with other criteria, (more symptoms, greater severity of symptoms) we could not find any effect of the intervention (post-hoc analysis, unpublished data).

The assessment that was a part of the intervention intended to capture treatable comorbidities such as anxiety, depression, pain and sleep disturbances. However, only a few patients actually had such comorbidities to a degree requiring treatment. Anxiety and depression are considered to be two important modifiable factors often found to affect the persistence of symptoms after mTBI (56, 161), but were, in fact, rare in the study group. Similarly, neither pain nor sleep problems were expressed at the intervention visit to the extent that they required treatment. This suggests that there might be other modifiable factors of interest to assess after mTBI.

One such modifiable factor could be visual changes after mTBI. Another possible modifiable factor could be fatigue, which was the most severe symptom in both randomized groups in our study, and which is often reported in other studies (7, 8, 58). Fatigue was not addressed in the present intervention. However, capturing different aspects of fatigue might have given a better basis for planning additional interventions, and in that way affecting outcome for the patients in the intervention group.

Reporting of symptoms after mTBI has also been suggested to be affected by pre-traumatic factors, including personal and social factors, and, therefore, a broader biopsychosocial

approach might have been more successful. Furthermore, the growing evidence shows that post-concussion symptoms are best described as an interaction between biological, psychological and social factors (57, 115, 162); and that not a single factor model, but a multidimensional approach, might be one way of finding predicting and modifiable factors (163).

One of the strengths of this study was the use of the ICF framework for the evaluation of outcome, including ICF components such as reported function (symptoms), activity and participation, thus making it possible to evaluate a component of rehabilitation medicine in Sweden; that is, to help the injured person to be able to be active and participate in the society despite having symptoms.

We have reported outcome regarding symptoms and disability at 3 months after mTBI. Therefore, conclusions cannot be drawn regarding the long-term effects of this early intervention, we can only speculate about the outcomes beyond the 3 months follow-up.

Patients with complaints after mTBI present to health care providers at different times after the injury: early, at acute or sub-acute stage or later, sometimes after many months. Clinicians have to rule out alternative medical conditions and explanations that may account for continuing problems after mTBI, especially in the chronic stages; there is a risk that symptoms may be erroneously attributed to mTBI, and other treatable pathologies may be overlooked.

5.2 STRATIFICATION OF PATIENTS BY SYMPTOMS EARLY AFTER mTBI

Despite many years of research on mTBI, there are to date no commonly acceptable prognostic models that can identify patients who have a high risk for poor outcome, in the form of persisting symptoms and disability. Identifying high-risk group among patients with mTBI early after the injury is of a considerable importance for planning of adequate clinical management.

Previous studies have shown that reporting many symptoms early after mTBI is associated with more reported symptoms 3 months after injury (7, 52, 164, 165) and with a poor outcome (7, 58). Based on previous research, a cut-off of 3 or more symptoms at ten days after the injury was used in our study as a discriminating criterion for identifying patients at high risk for persisting problems after mTBI. This stratification in to groups with high or low risk for poor outcome was shown to have some prognostic value. Patients who reported few symptoms at an early stage after mTBI continued to report few symptoms. Furthermore, patients in the group with an estimated low risk for a bad outcome, the non-randomized group in our study, also showed only minor limitations in activity and participation, and rated their health-related quality of life as good. This gives some support for the hypothesis that reporting few symptoms early after mTBI is a good prognostic factor. These findings were in line with Stulemeijer et al. study of early prediction of favorable outcome (166).

Symptoms after mTBI are the primary reason why patients seek health care. However, even though self-reported complaints are important and have been shown to have a predictive value (at least for patients with few symptoms predicting a good outcome), assessment limited to delineating symptoms might be not sufficient to identify patients at need of intervention or follow-up. Possibly, a combination of reported symptoms and objective findings might serve as a basis for prediction of outcome and a plan for intervention. For example, pre-injury psychiatric history, peri-injury stress, personal factors and early objective measures of brain dysfunction might all contribute to a future prognostic model. The concept of early prediction of outcome, both poor and good, is continuously investigated in studies of mTBI (11, 164, 166-168). Predictors of incomplete recovery after mTBI, shown in several studies (11, 163, 167), could be considered as modifiable factors for the intervention. Ideally, the prognostic targets should be identified early after mTBI, in ED or in close proximity to discharge.

5.3 VISUAL CHANGES AFTER mTBI

Results of our study indicate that there are differences in visual measures between mTBI group and both control groups early after the injury. The mTBI group differed statistically significantly from non-injured control group regarding accommodation amplitude at a sub-acute stage after the injury. We found improvement of accommodation amplitude over time. However, there were more than half of the patients with mTBI who still had deviations in accommodation, meeting the criteria of accommodation insufficiency (AI) at follow-up, giving some support for accommodation as a potentially sensitive parameter for monitoring recovery after mTBI. This finding is in agreement with other studies (72, 78, 79, 81).

Our study did not confirm findings in other studies that reported receded near point of convergence in patients with visual complaints after mTBI (72, 78, 169). One explanation for no difference in NPC between mTBI and both control groups might be that patients have recovered spontaneously during the time period after the injury before the baseline NPC measurements. Another explanation might be that patients with mTBI were using more effort to achieve normal performance on NPC. However, more effort applied might indicate more reported symptoms on the CISS. This idea is supported by our observation that increased symptoms on CISS correlated with reduced fusion, the most important component in the convergence eye movement. At follow-up, there was a statistically significant improvement over time in NPC in the mTBI group, and symptoms reported in CISS also improved in the mTBI group at follow-up.

We did not find differences between the mTBI and control groups in most of the measures of the saccades in our study. It might be that saccadic eye movements were assessed too late, in the mTBI group, and the changes had already been normalized before the assessment at the sub-acute stage, in line with the results reported by Pearson et al. (84). In that study, boxers showed increased saccadic latency directly after a blow to the head during the fight, but after 12 days, saccadic latency returned to the pre-fight level.

It might be speculated that increased effort to perform as well as practically possible on saccadic tests is expressed in reporting more symptoms, and this might indicate that more brain regions are involved. This hypothesis of a relationship between abnormal eye movements and changes in functional neural networks after mTBI was supported in a study by Johnson et al. (69) In this study, individuals with sports-related concussion were assessed with fMRI and simultaneously induced saccadic tasks at 7 days after the injury. Concussed persons showed a significantly worse performance on saccadic tests, at the same time, fMRI showed involvement of more brain regions compared to healthy controls (69). Despite an improvement in saccadic tests performance, and some improvement on fMRI, concussed persons showed altered brain activation patterns on fMRI at 30 days after the injury (170).

Despite growing evidence that the oculomotor changes occur in patients with mTBI, there is a substantial heterogeneity in the design of studies assessing those changes, making it difficult to replicate the results (67). Study populations are usually small and have an inadequate description of the mTBI population and controls. There is no unified reporting of outcome measures; furthermore, different studies have different examining protocols and procedures with varying post-injury and follow-up periods (67).

5.4 FATIGUE AND COGNITIVE FATIGABILITY AFTER mTBI AND ASSOCIATIONS WITH VISUAL CHANGES

Fatigue is one of most common symptoms after mTBI (7, 8, 58). Assessment of fatigue is mostly based on self-reporting questionnaires, and as such is subjective. It could be speculated that assessing different aspects of fatigue, including the use of objective measures, could increase the possibility of individualizing treatment.

One of our main findings regarding fatigue was that patients with mTBI had significantly more objectively measurable cognitive fatigability and self-reported acquired fatigue at the sub-acute stage compared to trauma controls with non-head injury. One can speculate that these findings might be attributed to brain injury. However, those changes were transient; there was a statistically significant improvement in cognitive fatigability in the mTBI group at follow-up, and there were no longer differences regarding self-rated fatigue measures between the patients with mTBI and the orthopedic controls at follow-up.

Another important finding in patients with mTBI was a significant association between self-rated acquired fatigue and objectively measurable cognitive fatigability.

In patients with mTBI, associations were found during the sub-acute stage between acquired fatigue and prosaccade latency as well as between trait fatigue and antisaccades. The interpretation of these observations is difficult and need to be studied further. Generation of saccades involves several neural networks (68) that might be further affected in the already challenged brain after mTBI. It could be hypothesized that even subtle transient changes in visual networks could increase perceived fatigue.

6 LIMITATIONS

Recruitment of patients with mTBI to research studies is known to be difficult and subject to several pitfalls. This was also the case in the present studies. One of the problems encountered during recruitment of patients is recruitment bias; that is, the recruited patients are not representative of the patients with mTBI presenting in clinical settings, making it difficult to generalize the results. This problem becomes more obvious in studies in which narrow inclusion criteria are applied to potential study participants. Hence, persons with pre-injury comorbidities, such as psychiatric diseases or alcohol abuse, were excluded in our study. On the other hand, broad inclusion criteria would have made it difficult to interpret whether the symptoms the patient reports are due to the mTBI or due to the comorbidity.

Furthermore, patients who declined participation in studies I and II were younger and mostly men, affecting the generalizability of the results. Similarly, there was a majority of men with mTBI that declined participation in studies III and IV.

Furthermore, the mTBI sample in studies III and IV was small, leading to the increased risk of type II error, namely, a risk of not finding a true difference between the groups. In order to minimize effect of presbyopia, age of study participants in studies III and IV was restricted to 18-40 years. Therefore, the findings of these studies can be attributed only to a population of young adults suffering mTBI, limiting generalizability.

7 FUTURE STUDIES AND CLINICAL IMPLICATIONS

There is still a need for continuous development of prediction models useful in different settings, at the ED, by general practitioner and at the rehab-center. Therefore, future studies could focus on prediction models. It is suggested that a standardized unit of measures could be employed, based on known predictive factors is suggested, similarly to the existing model for TBI prognosis (117).

Further investigations are also needed in order to identify new modifiable factors and evaluate the effects of targeting these in interventions.

There is a lack of evidence on which to base the management of impaired visual functions after mTBI. However, considering theoretical models and existing smaller studies, albeit with a risk of bias, it might be reasonable to refer patients with visual complaints to a vision care specialist as a part of general management of mTBI. Further investigation of the role of fMRI after mTBI could increase understanding of the pathophysiology behind symptoms and the recovery process. Changes in functional connectivity and the resting state mode might better define affected networks after trauma related to visual changes and fatigue.

The findings in our study lend some support to the hypothesis that routine follow-up in all patients after mTBI is not necessary. Instead, attention should be paid to patients at risk for

persisting problems. Identification of these patients could include not only assessment of current symptoms, but also an individualized approach incorporating consideration of past medical history, medications and psychosocial situation, and capturing other pre-injury factors, such as coping strategies. This study did not attempt to assess personal factors. However, in the light of existing evidence that personal factors, such as coping strategies and illness perception, are associated with poor outcome (109), it would be appropriate to address coping strategies in future studies.

Health care professionals should ensure that accurate written educational information is given to all patients, both in the ED and at other healthcare services where patients might seek help at later time point after injury.

In Sweden, there is a need to develop evidence-based standardized clinical guidelines that should include recommendations on assessments in order to identify potential modifiable factors, where fatigue should be addressed and visual functions should not be overlooked.

8 CONCLUSIONS

- An early individualized educational follow-up visit offered to patients with many symptoms early after mTBI, at risk for persisting disability, had no effect on symptom level, quality of life, activity and participation 3 months after the mTBI.
- The results of this study lend some support to previous findings that patients reporting no or few symptoms early after mTBI have a good outcome, and thus have low risk for persisting disability and no need for routine follow-up.
- There were some transient measurable visual changes regarding convergence in patients with mTBI during the sub-acute period after the injury. The finding of association between visual symptoms and fusional vergence requires further evaluation.
- The results of this study lend some support to the value of assessing different aspects of fatigue. At the same time, it is important to understand what aspects of fatigue different assessment instruments measure. We did not find a distinct association between visual measures and fatigue. Findings regarding associations between saccades and fatigue are difficult to interpret.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

De flesta som drabbas av en hjärnskakning eller lätt traumatisk hjärnskada återhämtar sig ganska snabbt men en del får besvär under en längre tid. I dag finns ingen gängse uppföljning efter en lätt traumatisk hjärnskada eller rekommenderad behandling för de personer som får långvariga besvär. För att undvika onödiga sjukvårdsbesök och för att åstadkomma en kostnadseffektiv uppföljning efter lätt traumatisk hjärnskada bör insatser riktas till personer som har en trolig risk för långvariga besvär.

I en randomiserad kontrollerad multicenterstudie utvärderades en tidig intervention given till personer med bedömt ökad risk, baserat på symtomskattning, för långvariga besvär efter en lätt traumatisk hjärnskada. Patienter som bedömdes ha en hög risk för långvariga besvär randomiserades till interventionsgrupp eller till konventionell handläggning. Den intervention som gavs inkluderade förutom lugnande besked om en troligt god prognos, även en strukturerad anamnes, undersökning av nervstatus, och vid behov, förslag på behandling av besvär såsom ångest, depression eller smärta.

Uppföljning av alla studiedeltagare skedde efter ca tre månader. Ingen effekt av den givna behandlingen kunde påvisas baserat på symtomskattning, påverkan på aktivitetsutförande och på skattning av livskvalitet. Endast få personer hade sjukskrivning som var längre än 3 månader. De patienter som hade få symptom i tidigt skede efter hjärnskakningen, fortsatte att ha få symptom och hade inte heller några problem med aktiviteter i vardagen samt de skattade sin livskvalitet högt. Tolkningen av detta är att stratifiering efter antal symtom kan vara en bra modell för att identifiera personer som inte behöver någon strukturerad uppföljning efter lätt traumatisk hjärnskada.

För att öka kunskapen om potentiellt behandlingsbara faktorer undersöktes visuella symtom och visuella funktioner samt trötthet och i test mätbar uttröttbarhet hos 15 patienter med lätt traumatisk hjärnskada och i två kontrollgrupper med 15 patienter som sökt på akuten med extremitetsskada och 15 oskadade personer. Alla deltagare undersöktes och svarade på frågeformulär vid två tillfällen, i tidigt skede, ca 10 dagar efter traumat och efter ca 3-4 månader.

Patienter med hjärnskakning hade övergående subjektiva och vissa mätbara objektiva visuella förändringar, samt övergående nytillkommen trötthet. Det fanns även en association mellan nytillkommen trötthet och i test mätbar uttröttbarhet. Dessa fynd behöver valideras i större studier för att kunna implementeras i omhändertagandet av patienter med lätt traumatisk hjärnskada.

10 ACKNOWLEDGEMENTS

There are many people that I would like to thank for their contribution to this thesis and for their support.

I would like to express my sincerely gratitude to the patients and control subjects for their kind participation in both clinical studies that these theses are based upon.

My thank goes to the Division of Rehabilitation Medicine and Department of Clinical sciences at Karolinska Institutet that made my research possible.

This thesis would not be finished successfully without the help of my supervisors and co-authors.

First of all, I would like to thank Catharina de Boussard, my principal supervisor, for continuous encouragement and positive attitude towards my scientific education, for possibility to carry out my research and combine it with clinical work, for endless after-work working, with or without birds chirping and singing in the background, and for her enormous flexibility in supervising.

I express my gratitude to my co-supervisor Alison Godbolt for her careful attention to details and expanding my ability to critical thinking and evaluating the best evidence.

I wish to express my sincere gratitude to my co-supervisor professor Jörgen Borg for kindly sharing his profound knowledge in the field of mild traumatic brain injury and for his expert support.

I would like to thank my co-authors and to acknowledge their contributions to the studies included in this thesis:

Professor Britt Marie Stålnacke for valuable help throughout the work with the intervention study, Dr. Trandur Ulfarsson for his support during the writing of the manuscript, Associated professor Gunilla Eriksson for sharing with me her expertise in the research on activity and participation, Dr. Marika Möller for introducing to fatigue research.

My special thanks go to my co-authors Jan Johansson and Tony Pansell for introducing me in to the wonderful world of vision, for positive thinking and making me believe that research is a joy. I wish to express my special thanks to Jan Johansson for his amazing flexibility and patience during writing and revising the manuscript, and for inspirational discussions.

Professor Kristina Alexandersson for introducing me to the research of sickness absence. Professor Staffan Marklund for tutoring during the course in Insurance Medicine.

Ssk Seija Lund, ssk Sandra Hallström and all collaborators in Swedish Intervention study on Concussion SIC. Ssk Anna Hedenäs for excellent assistance in collecting patients data in Vision study, and keeping “ajour” with changes during recruitment of study participants.

Gunnar Edman, for all help with statistics in the intervention study.

Lisbet Broman, for the excellent help with data analysis and introducing to the endless possibilities of SPSS.

Per Näsman, for his help with statistical analysis in vision study.

Stefan Arousel, for always finding a design solution, even for impossible tasks.

My supervisors at KI Immunology department in the 1990s:

Professor Annika Scheynius, for accepting me to her research group and encouraging me to be open minded for research horizons. Ingeborg van der Ploeg, for generously supervising me from simple lab tricks to practical “new in Sweden” matters.

My fellow doctoral students, now and then at the Division of Rehabilitation Medicine: Dr. Gabriela Markovic, for generously sharing food and mood, and her experiences as doctoral student, Christian Oldenburg, for valuable discussions, especially on mTBI matters, Gaia Penatti, thank you for learning me one or two Italian words, Jeanette Plantin, Anneli Wall, Dr. Katarina Skough Vrede for research discussions.

I wish to express my sincere thanks to my colleagues and co-workers at the Clinic of Rehabilitation Medicine:

Anna Tölli, for clinical supervision during my residency in Rehabilitation Medicine and for encouragement to follow my clinical research dream.

My colleagues physicians who shared their knowledge and experiences during my clinical work: Märta Berthold Lindstedt, Carin Persson, Monica von Heijne, Per Broman, Jana Randman, Annette Juvall, Ada Slowinska, Ivan Sunara, Marita Bengstsson, Charikleia Pappa, Carin von Grothusen, Eva Melin, Vera Häglund, Ingrid Rydmark, Karin Uhlin.

My special thanks go to co-workers in outpatient rehabilitation teams at Danderyd and at Huddinge hospitals.

My sincere thanks go to my fantastic friends in Lithuania and in Sweden: Aušra, for being my friend over many years, sharing dreams and simple students meals in Kauno Medicinos institutas, and always encouraging me with: “there is nothing we, ladies, can’t achieve”; Jolanta, Dangira, Daiva for being always there; Prima, for tutoring me in life and research matters; Monica, for wise words and encouragement, Marine, Helena, for friendly talks and walks round “lago maggiore”, Olga, Maria and “grand dame” Olga Samuilovna, for cozy dinners and discussions; Fatma and Hayet, for calmly chats;

Dalia ir Vidas – for many years of friendship, sharing endless family dinners and challenging walks in the woods – with or without their skillfully prepared orientation maps.

I am deeply grateful to my family:

My parents Regina and Antanas, my brother Rimas and his family, my godmother Milda for love and support,

My beloved sons Justas and Marius for just being wonderful young men," teasing me softly", always with a smile and a big hug, and for introducing Lina to our boyish family,

My husband Darius for never ending love, support and for always believing in me.

11 REFERENCES

1. The Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA: Centers for Disease Control and Prevention: National Center for Injury Prevention and Control, part of the Centers for Disease Control and Prevention, 1993.

2. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.

3. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):28-60.

4. Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):84-105.

5. Stalnacke BM, Bjornstig U, Karlsson K, Sojka P. One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase. J Rehabil Med. 2005;37(5):300-5.

6. Ruff R. Two decades of advances in understanding of mild traumatic brain injury. The Journal of head trauma rehabilitation. 2005;20(1):5-18.

7. Lundin A, de Boussard C, Edman G, Borg J. Symptoms and disability until 3 months after mild TBI. Brain Inj. 2006;20(8):799-806.

8. Lannsjo M, af Geijerstam JL, Johansson U, Bring J, Borg J. Prevalence and structure of symptoms at 3 months after mild traumatic brain injury in a national cohort. Brain Inj. 2009;23(3):213-9.

9. Sigurdardottir S, Andelic N, Roe C, Jerstad T, Schanke AK. Post-concussion symptoms after traumatic brain injury at 3 and 12 months post-injury: a prospective study. Brain Inj. 2009;23(6):489-97.

10. Roe C, Sveen U, Alvsaker K, Bautz-Holter E. Post-concussion symptoms after mild traumatic brain injury: influence of demographic factors and injury severity in a 1-year cohort study. Disabil Rehabil. 2009;31(15):1235-43.

11. Hou R, Moss-Morris R, Peveler R, Mogg K, Bradley BP, Belli A. When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. Journal of neurology, neurosurgery, and psychiatry. 2012;83(2):217-23.

12. McMahon P, Hricik A, Yue JK, Puccio AM, Inoue T, Lingsma HF, et al. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. Journal of neurotrauma. 2014;31(1):26-33.

13. de Koning ME, Scheenen ME, van der Horn HJ, Hageman G, Roks G, Yilmaz T, et al. Outpatient follow-up after mild traumatic brain injury: Results of the UPFRONT-study. Brain Inj. 2017;31(8):1102-8.

14. Nygren-de Boussard C, Holm LW, Cancelliere C, Godbolt AK, Boyle E, Stalnacke BM, et al. Nonsurgical interventions after mild traumatic brain injury: a systematic review. Results

of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014;95(3 Suppl):S257-64.

15. Ruff RM, Iverson GL, Barth JT, Bush SS, Broshek DK. Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2009;24(1):3-10.

16. Iverson G, Lange R, Gaetz M, Zasler N. Mild traumatic brain injury. In: Zasler N, Katz D, Zafonte R, editors. Brain injury medicine: Principles and practice. New York: Demos Medical Publishing; 2013.

17. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):113-25.

18. The American Congress of Rehabilitation Medicine. Mild Traumatic Brain

Injury Committee of the Head Injury Interdisciplinary Special Interest

Group of the American Congress of Rehabilitation Medicine. Definition of

mild traumatic brain injury. . The Journal of head trauma rehabilitation. 1993;8:86-7.

19. Iverson GL. Outcome from mild traumatic brain injury. Curr Opin Psychiatry. 2005;18(3):301-17.

20. Borg J, Holm L, Cassidy JD, Peloso PM, Carroll LJ, von Holst H, et al. Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):61-75.

21. McCrory P, Feddermann-Demont N, Dvorak J, Cassidy JD, McIntosh A, Vos PE, et al. What is the definition of sports-related concussion: a systematic review. British journal of sports medicine. 2017;51(11):877-87.

22. Chapman JC, Diaz-Arrastia R. Military traumatic brain injury: a review. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2014;10(3 Suppl):S97-104.

23. Bazarian JJ, McClung J, Shah MN, Cheng YT, Flesher W, Kraus J. Mild traumatic brain injury in the United States, 1998--2000. Brain Inj. 2005;19(2):85-91.

24. Statistics database for statistics on injury and injury events in Sweden's municipalities and counties. In: Welfare SNBoHa, editor. 2017.

25. af Geijerstam JL, Oredsson S, Britton M. Medical outcome after immediate computed tomography or admission for observation in patients with mild head injury: randomised controlled trial. BMJ (Clinical research ed). 2006;333(7566):465.

26. Borg J, Roe C, Nordenbo A, Andelic N, de Boussard C, af Geijerstam JL. Trends and challenges in the early rehabilitation of patients with traumatic brain injury: a Scandinavian perspective. American journal of physical medicine & rehabilitation. 2011;90(1):65-73.

27. Injury-related visits to emergency department. In: Welfare NBoHa, editor. Injury Database2011.

28. Kristman VL, Borg J, Godbolt AK, Salmi LR, Cancelliere C, Carroll LJ, et al. Methodological issues and research recommendations for prognosis after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014;95(3 Suppl):S265-77.

29. International classification of functioning, disability and health, ICF, (2001).

30. Lexell J, Brogardh C. The use of ICF in the neurorehabilitation process. NeuroRehabilitation. 2015;36(1):5-9.

31. Sveen U, Ostensjo S, Laxe S, Soberg HL. Problems in functioning after a mild traumatic brain injury within the ICF framework: the patient perspective using focus groups. Disabil Rehabil. 2013;35(9):749-57.

32. Blyth BJ, Bazarian JJ. Traumatic alterations in consciousness: traumatic brain injury. Emergency medicine clinics of North America. 2010;28(3):571-94.

33. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery. 2014;75 Suppl 4:S24-33.

34. Jassam YN, Izzy S, Whalen M, McGavern DB, El Khoury J. Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift. Neuron. 2017;95(6):1246-65.

35. Signoretti S, Vagnozzi R, Tavazzi B, Lazzarino G. Biochemical and neurochemical sequelae following mild traumatic brain injury: summary of experimental data and clinical implications. Neurosurgical focus. 2010;29(5):E1.

36. Choe MC. The Pathophysiology of Concussion. Current pain and headache reports. 2016;20(6):42.

37. Zetterberg H, Blennow K. Fluid markers of traumatic brain injury. Molecular and cellular neurosciences. 2015;66(Pt B):99-102.

38. Anderson RE, Hansson LO, Nilsson O, Dijlai-Merzoug R, Settergren G. High serum S100B levels for trauma patients without head injuries. Neurosurgery. 2001;48(6):1255-8; discussion 8-60.

39. Stalnacke BM, Ohlsson A, Tegner Y, Sojka P. Serum concentrations of two biochemical markers of brain tissue damage S-100B and neurone specific enolase are increased in elite female soccer players after a competitive game. British journal of sports medicine. 2006;40(4):313-6.

40. Agoston DV, Shutes-David A, Peskind ER. Biofluid biomarkers of traumatic brain injury. Brain Inj. 2017;31(9):1195-203.

41. FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults, (2018).

42. Yuh EL, Hawryluk GW, Manley GT. Imaging concussion: a review. Neurosurgery. 2014;75 Suppl 4:S50-63.

43. Mayer AR, Bellgowan PS, Hanlon FM. Functional magnetic resonance imaging of mild traumatic brain injury. Neuroscience and biobehavioral reviews. 2015;49:8-18.

44. van der Horn HJ, Liemburg EJ, Scheenen ME, de Koning ME, Spikman JM, van der Naalt J. Post-concussive complaints after mild traumatic brain injury associated with altered brain networks during working memory performance. Brain imaging and behavior. 2016;10(4):1243-53.

45. Johnson B, Zhang K, Gay M, Horovitz S, Hallett M, Sebastianelli W, et al. Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. NeuroImage. 2012;59(1):511-8.

46. van der Horn HJ, Scheenen ME, de Koning ME, Liemburg EJ, Spikman JM, van der Naalt J. The Default Mode Network as a Biomarker of Persistent Complaints after Mild Traumatic Brain Injury: A Longitudinal Functional Magnetic Resonance Imaging Study. Journal of neurotrauma. 2017;34(23):3262-9.

47. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.

48. American Psychiatric Association. DSM IV. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

49. American Psychiatric Association. DSM V. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013.

50. Iverson GL, McCracken LM. 'Postconcussive' symptoms in persons with chronic pain. Brain Inj. 1997;11(11):783-90.

51. Iverson GL, Lange RT. Examination of "postconcussion-like" symptoms in a healthy sample. Applied neuropsychology. 2003;10(3):137-44.

52. Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A, Schonberger M. Predictors of postconcussive symptoms 3 months after mild traumatic brain injury. Neuropsychology. 2012;26(3):304-13.

53. Meares S, Shores EA, Taylor AJ, Batchelor J, Bryant RA, Baguley IJ, et al. The prospective course of postconcussion syndrome: the role of mild traumatic brain injury. Neuropsychology. 2011;25(4):454-65.

54. Iverson GL. Misdiagnosis of the persistent postconcussion syndrome in patients with depression. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. 2006;21(4):303-10.

55. Lange RT, Iverson GL, Rose A. Depression strongly influences postconcussion symptom reporting following mild traumatic brain injury. The Journal of head trauma rehabilitation. 2011;26(2):127-37.

56. Levin HS, McCauley SR, Josic CP, Boake C, Brown SA, Goodman HS, et al. Predicting depression following mild traumatic brain injury. Archives of general psychiatry. 2005;62(5):523-8.

57. Cassidy JD, Cancelliere C, Carroll LJ, Cote P, Hincapie CA, Holm LW, et al. Systematic review of self-reported prognosis in adults after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014;95(3 Suppl):S132-51.

58. Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A. Long-term outcomes after uncomplicated mild traumatic brain injury: a comparison with trauma controls. Journal of neurotrauma. 2011;28(6):937-46.

59. Kraus JF, Hsu P, Schafer K, Afifi AA. Sustained outcomes following mild traumatic brain injury: results of a five-emergency department longitudinal study. Brain Inj. 2014;28(10):1248-56.

60. de Koning ME, Gareb B, El Moumni M, Scheenen ME, van der Horn HJ, Timmerman ME, et al. Subacute posttraumatic complaints and psychological distress in trauma patients with or without mild traumatic brain injury. Injury. 2016;47(9):2041-7.

61. Snell DL, Siegert RJ, Hay-Smith EJ, Surgenor LJ. Associations between illness perceptions, coping styles and outcome after mild traumatic brain injury: preliminary results from a cohort study. Brain Inj. 2011;25(11):1126-38.

62. Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, et al. Factors influencing outcome following mild traumatic brain injury in adults. Journal of the International Neuropsychological Society : JINS. 2000;6(5):568-79.

63. Bazarian JJ, Blyth B, Mookerjee S, He H, McDermott MP. Sex differences in outcome after mild traumatic brain injury. Journal of neurotrauma. 2010;27(3):527-39.

64. Meares S, Shores EA, Taylor AJ, Batchelor J, Bryant RA, Baguley IJ, et al. Mild traumatic brain injury does not predict acute postconcussion syndrome. Journal of neurology, neurosurgery, and psychiatry. 2008;79(3):300-6.

65. Mickeviciene D, Schrader H, Obelieniene D, Surkiene D, Kunickas R, Stovner LJ, et al. A controlled prospective inception cohort study on the post-concussion syndrome outside the medicolegal context. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2004;11(6):411-9.

66. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. The Lancet Neurology. 2014;13(10):1006-16.

67. Hunt AW, Mah K, Reed N, Engel L, Keightley M. Oculomotor-Based Vision Assessment in Mild Traumatic Brain Injury: A Systematic Review. The Journal of head trauma rehabilitation. 2016;31(4):252-61.

68. Tyler CW, Likova LT, Mineff KN, Nicholas SC. Deficits in the Activation of Human Oculomotor Nuclei in Chronic Traumatic Brain Injury. Frontiers in neurology. 2015;6:173.

69. Johnson B, Zhang K, Hallett M, Slobounov S. Functional neuroimaging of acute oculomotor deficits in concussed athletes. Brain imaging and behavior. 2015;9(3):564-73.

70. Ting WK, Schweizer TA, Topolovec-Vranic J, Cusimano MD. Antisaccadic Eye Movements Are Correlated with Corpus Callosum White Matter Mean Diffusivity, Stroop Performance, and Symptom Burden in Mild Traumatic Brain Injury and Concussion. Frontiers in neurology. 2015;6:271.

71. Ciuffreda KJ, Kapoor N, Rutner D, Suchoff IB, Han ME, Craig S. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry (St Louis, Mo). 2007;78(4):155-61.

72. Brahm KD, Wilgenburg HM, Kirby J, Ingalla S, Chang CY, Goodrich GL. Visual impairment and dysfunction in combat-injured servicemembers with traumatic brain injury. Optometry and vision science : official publication of the American Academy of Optometry. 2009;86(7):817-25.

73. Greenwald BD, Kapoor N, Singh AD. Visual impairments in the first year after traumatic brain injury. Brain Inj. 2012;26(11):1338-59.

74. Hokoda SC. General binocular dysfunctions in an urban optometry clinic. Journal of the American Optometric Association. 1985;56(7):560-2.

75. Porcar E, Martinez-Palomera A. Prevalence of general binocular dysfunctions in a population of university students. Optometry and vision science : official publication of the American Academy of Optometry. 1997;74(2):111-3.

76. Lara F, Cacho P, Garcia A, Megias R. General binocular disorders: prevalence in a clinic population. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists). 2001;21(1):70-4.

77. Heitger MH, Jones RD, Macleod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. Brain : a journal of neurology. 2009;132(Pt 10):2850-70.

78. Capo-Aponte JE, Urosevich TG, Temme LA, Tarbett AK, Sanghera NK. Visual dysfunctions and symptoms during the subacute stage of blast-induced mild traumatic brain injury. Military medicine. 2012;177(7):804-13.

79. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential eye movements in mild traumatic brain injury versus normal controls. The Journal of head trauma rehabilitation. 2015;30(1):21-8.

80. Hellerstein LF, Freed S, Maples WC. Vision profile of patients with mild brain injury. Journal of the American Optometric Association. 1995;66(10):634-9.

81. Green W, Ciuffreda KJ, Thiagarajan P, Szymanowicz D, Ludlam DP, Kapoor N. Accommodation in mild traumatic brain injury. Journal of rehabilitation research and development. 2010;47(3):183-99.

82. Magone MT, Kwon E, Shin SY. Chronic visual dysfunction after blast-induced mild traumatic brain injury. Journal of rehabilitation research and development. 2014;51(1):71-80.

83. Heitger MH, Anderson TJ, Jones RD, Dalrymple-Alford JC, Frampton CM, Ardagh MW. Eye movement and visuomotor arm movement deficits following mild closed head injury. Brain : a journal of neurology. 2004;127(Pt 3):575-90.

84. Pearson BC, Armitage KR, Horner CW, Carpenter RH. Saccadometry: the possible application of latency distribution measurement for monitoring concussion. British journal of sports medicine. 2007;41(9):610-2.

85. Maruta J, Spielman LA, Yarusi BB, Wang Y, Silver JM, Ghajar J. Chronic Post-Concussion Neurocognitive Deficits. II. Relationship with Persistent Symptoms. Frontiers in human neuroscience. 2016;10:45.

86. Ciuffreda KJ, Ludlam DP, Thiagarajan P, Yadav NK, Capo-Aponte J. Proposed objective visual system biomarkers for mild traumatic brain injury. Military medicine. 2014;179(11):1212-7.

87. Mullen SJ, Yucel YH, Cusimano M, Schweizer TA, Oentoro A, Gupta N. Saccadic eye movements in mild traumatic brain injury: a pilot study. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2014;41(1):58-65.

88. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. Neurology. 2013;80(4):409-16.

89. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet. 2004;363(9413):978-88.

90. Jason LA, Evans M, Brown M, Porter N. What is fatigue? Pathological and nonpathological fatigue. PM & R : the journal of injury, function, and rehabilitation. 2010;2(5):327-31.

91. Cantor JB, Ashman T, Gordon W, Ginsberg A, Engmann C, Egan M, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life. The Journal of head trauma rehabilitation. 2008;23(1):41-51.

92. Norrie J, Heitger M, Leathem J, Anderson T, Jones R, Flett R. Mild traumatic brain injury and fatigue: a prospective longitudinal study. Brain Inj. 2010;24(13-14):1528-38.

93. Wylie G, Flashman L. Understanding the interplay between mild traumatic brain injury and cognitive fatigue: models and treatments. Concussion/Future Medicine. 2017;2(4).

94. de Leon MB, Kirsch NL, Maio RF, Tan-Schriner CU, Millis SR, Frederiksen S, et al. Baseline predictors of fatigue 1 year after mild head injury. Archives of physical medicine and rehabilitation. 2009;90(6):956-65.

95. Johansson B, Berglund P, Ronnback L. Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. Brain Inj. 2009;23(13-14):1027-40.

96. Ziino C, Ponsford J. Selective attention deficits and subjective fatigue following traumatic brain injury. Neuropsychology. 2006;20(3):383-90.

97. van der Linden D, Frese M, Meijman TF. Mental fatigue and the control of cognitive processes: effects on perseveration and planning. Acta psychologica. 2003;113(1):45-65.

98. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of neurology. 1989;46(10):1121-3.

99. Moller MC, Nygren de Boussard C, Oldenburg C, Bartfai A. An investigation of attention, executive, and psychomotor aspects of cognitive fatigability. Journal of clinical and experimental neuropsychology. 2014;36(7):716-29.

100. Emanuelson I, Andersson Holmkvist E, Bjorklund R, Stalhammar D. Quality of life and post-concussion symptoms in adults after mild traumatic brain injury: a population-based study in western Sweden. Acta neurologica Scandinavica. 2003;108(5):332-8.

101. Law M. Participation in the occupations of everyday life. The American journal of occupational therapy : official publication of the American Occupational Therapy Association. 2002;56(6):640-9.

102. Cancelliere C, Kristman VL, Cassidy JD, Hincapie CA, Cote P, Boyle E, et al. Systematic review of return to work after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014;95(3 Suppl):S201-9.

103. van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. Journal of neurology, neurosurgery, and psychiatry. 1999;66(2):207-13.

104. Waljas M, Iverson GL, Lange RT, Liimatainen S, Hartikainen KM, Dastidar P, et al. Return to work following mild traumatic brain injury. The Journal of head trauma rehabilitation. 2014;29(5):443-50.

105. Elgmark Andersson E, Emanuelson I, Bjorklund R, Stalhammar DA. Mild traumatic brain injuries: the impact of early intervention on late sequelae. A randomized controlled trial. Acta neurochirurgica. 2007;149(2):151-9.

106. Wrightson P, Gronwall D. Time off work and symptoms after minor head injury. Injury. 1981;12(6):445-54.

107. Mah K, Hickling A, Reed N. Perceptions of mild traumatic brain injury in adults: a scoping review. Disabil Rehabil. 2018;40(8):960-73.

108. Scheenen ME, Spikman JM, de Koning ME, van der Horn HJ, Roks G, Hageman G, et al. Patients "At Risk" of Suffering from Persistent Complaints after Mild Traumatic Brain Injury: The Role of Coping, Mood Disorders, and Post-Traumatic Stress. Journal of neurotrauma. 2017;34(1):31-7.

109. Maestas KL, Sander AM, Clark AN, van Veldhoven LM, Struchen MA, Sherer M, et al. Preinjury coping, emotional functioning, and quality of life following uncomplicated and complicated mild traumatic brain injury. The Journal of head trauma rehabilitation. 2014;29(5):407-17.

110. Whittaker R, Kemp S, House A. Illness perceptions and outcome in mild head injury: a longitudinal study. Journal of neurology, neurosurgery, and psychiatry. 2007;78(6):644-6.

111. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Social science & medicine (1982). 1995;41(10):1403-9.

112. Polinder S, Haagsma JA, van Klaveren D, Steyerberg EW, van Beeck EF. Health-related quality of life after TBI: a systematic review of study design, instruments, measurement properties, and outcome. Population health metrics. 2015;13:4.

113. Cieza A, Stucki G. Content comparison of health-related quality of life (HRQOL) instruments based on the international classification of functioning, disability and health (ICF). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2005;14(5):1225-37.

114. Silverberg ND, Iverson GL. Etiology of the post-concussion syndrome: Physiogenesis and Psychogenesis revisited. NeuroRehabilitation. 2011;29(4):317-29.

115. Iverson G, Silverberg N, Lange R, Zasler N. Conceptualizing outcome from mild traumatic brain injury. In: Zasler N, Katz D, Zafonte R, editors. Brain injury medicine: Principles and practice. New York Demos Medical Publishing; 2013.

116. Cole W, Bailie J. Neurocognitive and Psychiatric Symptoms following Mild Traumatic Brain Injury. In: Laskowitz D, Grant G, editors. Translational Research in Traumatic Brain Injury. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016.

117. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS medicine. 2008;5(8):e165; discussion e.

118. Wang L, Yu C, Chen H, Qin W, He Y, Fan F, et al. Dynamic functional reorganization of the motor execution network after stroke. Brain : a journal of neurology. 2010;133(Pt 4):1224-38.

119. Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nature neuroscience. 2012;15(4):528-36.

120. Nudo RJ. Recovery after brain injury: mechanisms and principles. Frontiers in human neuroscience. 2013;7:887.

121. Carroll LJ, Cassidy JD, Cancelliere C, Cote P, Hincapie CA, Kristman VL, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild

Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014;95(3 Suppl):S152-73.

122. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. Journal of the International Neuropsychological Society : JINS. 2005;11(3):215-27.

123. Gravel J, D'Angelo A, Carriere B, Crevier L, Beauchamp MH, Chauny JM, et al. Interventions provided in the acute phase for mild traumatic brain injury: a systematic review. Systematic reviews. 2013;2:63.

124. Ruff RM. Mild traumatic brain injury and neural recovery: rethinking the debate. NeuroRehabilitation. 2011;28(3):167-80.

125. Levin HS, Diaz-Arrastia RR. Diagnosis, prognosis, and clinical management of mild traumatic brain injury. The Lancet Neurology. 2015;14(5):506-17.

126. Unden J, Ingebrigtsen T, Romner B. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC medicine. 2013;11:50.

127. Borg J, Holm L, Peloso PM, Cassidy JD, Carroll LJ, von Holst H, et al. Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):76-83.

128. Eliyahu L, Kirkland S, Campbell S, Rowe BH. The Effectiveness of Early Educational Interventions in the Emergency Department to Reduce Incidence or Severity of Postconcussion Syndrome Following a Concussion: A Systematic Review. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2016;23(5):531-42.

129. Bell KR, Hoffman JM, Temkin NR, Powell JM, Fraser RT, Esselman PC, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. Journal of neurology, neurosurgery, and psychiatry. 2008;79(11):1275-81.

130. Suffoletto B, Wagner AK, Arenth PM, Calabria J, Kingsley E, Kristan J, et al. Mobile phone text messaging to assess symptoms after mild traumatic brain injury and provide self-care support: a pilot study. The Journal of head trauma rehabilitation. 2013;28(4):302-12.

131. Belanger HG, Barwick F, Silva MA, Kretzmer T, Kip KE, Vanderploeg RD. Web-based psychoeducational intervention for postconcussion symptoms: a randomized trial. Military medicine. 2015;180(2):192-200.

132. Ghaffar O, McCullagh S, Ouchterlony D, Feinstein A. Randomized treatment trial in mild traumatic brain injury. Journal of psychosomatic research. 2006;61(2):153-60.

133. Vikane E, Hellstrom T, Roe C, Bautz-Holter E, Assmus J, Skouen JS. Multidisciplinary outpatient treatment in patients with mild traumatic brain injury: A randomised controlled intervention study. Brain Inj. 2017;31(4):475-84.

134. Potter S, Brown RG. Cognitive behavioural therapy and persistent post-concussional symptoms: integrating conceptual issues and practical aspects in treatment. Neuropsychological rehabilitation. 2012;22(1):1-25.

135. Bergersen K, Halvorsen JO, Tryti EA, Taylor SI, Olsen A. A systematic literature review of psychotherapeutic treatment of prolonged symptoms after mild traumatic brain injury. Brain Inj. 2017;31(3):279-89.

136. Scheenen ME, Visser-Keizer AC, de Koning ME, van der Horn HJ, van de Sande P, van Kessel M, et al. Cognitive Behavioral Intervention Compared to Telephone Counseling Early after Mild Traumatic Brain Injury: A Randomized Trial. Journal of neurotrauma. 2017;34(19):2713-20.

137. de Kruijk JR, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. Journal of neurology, neurosurgery, and psychiatry. 2002;73(2):167-72.

138. Fann JR, Uomoto JM, Katon WJ. Sertraline in the treatment of major depression following mild traumatic brain injury. The Journal of neuropsychiatry and clinical neurosciences. 2000;12(2):226-32.

139. Fann JR, Uomoto JM, Katon WJ. Cognitive improvement with treatment of depression following mild traumatic brain injury. Psychosomatics. 2001;42(1):48-54.

140. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. Annals of internal medicine. 2008;148(4):W60-6.

141. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. Journal of neurology. 1995;242(9):587-92.

142. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.

143. Eriksson G, Tham K, Kottorp A. A cross-diagnostic validation of an instrument measuring participation in everyday occupations: the Occupational Gaps Questionnaire (OGQ). Scandinavian journal of occupational therapy. 2013;20(2):152-60.

144. Crawford S, Wenden FJ, Wade DT. The Rivermead head injury follow up questionnaire: a study of a new rating scale and other measures to evaluate outcome after head injury. Journal of neurology, neurosurgery, and psychiatry. 1996;60(5):510-4.

145. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992;30(6):473-83.

146. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Social science & medicine (1982). 1995;41(10):1349-58.

147. Eyres S, Carey A, Gilworth G, Neumann V, Tennant A. Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire. Clinical rehabilitation. 2005;19(8):878-87.

148. Potter S, Leigh E, Wade D, Fleminger S. The Rivermead Post Concussion Symptoms Questionnaire: a confirmatory factor analysis. Journal of neurology. 2006;253(12):1603-14.

149. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. Journal of psychosomatic research. 2002;52(2):69-77.

150. Scheiman M, Wick B. Clinical management of binocular vision: heterophoric, accommodative, and eye movement disorders. 4th ed. ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014.

151. Borsting EJ, Rouse MW, Mitchell GL, Scheiman M, Cotter SA, Cooper J, et al. Validity and reliability of the revised convergence insufficiency symptom survey in children aged 9 to

18 years. Optometry and vision science : official publication of the American Academy of Optometry. 2003;80(12):832-8.

152. Rouse MW, Borsting EJ, Mitchell GL, Scheiman M, Cotter SA, Cooper J, et al. Validity and reliability of the revised convergence insufficiency symptom survey in adults. Ophthalmic & physiological optics : the journal of the British College of Ophthalmic Opticians (Optometrists). 2004;24(5):384-90.

153. Wechsler D. WAIS-III Svensk version (M. Hagelthorn, Trans.). Stockholm: Psykologiförlaget; 2003.

154. Ruff R, Allen C. Ruff 2 & 7 Selective Attention Test. Lutz: Psychological Assessment Resources, Inc.; 1996.

155. Kaplan E, Fein D, Morris R, Delis D. WAIS-R NI. WAIS-R som neuropsykologiskt instrument. Manual. A. Bartfai, H. Nyman & B. Stegman, Trans. Stockholm: Psykologiförlaget; 1994.

156. Lezak M, Howieson D, Bigler E. Neuropsychological Assessment 5th ed. New York: Oxford University Press; 2012.

157. Almkvist O, Adveen M, Henning L, Tallberg IM. Estimation of premorbid cognitive function based on word knowledge: the Swedish Lexical Decision Test (SLDT). Scandinavian journal of psychology. 2007;48(3):271-9.

158. Matuseviciene G. Sickness absence in patients with mild traumatic brain injury (MTBI) in Sweden. Course paper (6 ECT) at an insurance medicine course. KI: Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, 2014.

159. Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, et al. Impact of early intervention on outcome following mild head injury in adults. Journal of neurology, neurosurgery, and psychiatry. 2002;73(3):330-2.

160. Snell DL, Surgenor LJ, Hay-Smith EJ, Siegert RJ. A systematic review of psychological treatments for mild traumatic brain injury: an update on the evidence. Journal of clinical and experimental neuropsychology. 2009;31(1):20-38.

161. Mollayeva T, D'Souza A, Mollayeva S. Sleep and Psychiatric Disorders in Persons With Mild Traumatic Brain Injury. Current psychiatry reports. 2017;19(8):47.

162. Waljas M, Lange RT, Hakulinen U, Huhtala H, Dastidar P, Hartikainen K, et al. Biopsychosocial outcome after uncomplicated mild traumatic brain injury. Journal of neurotrauma. 2014;31(1):108-24.

163. Silverberg ND, Gardner AJ, Brubacher JR, Panenka WJ, Li JJ, Iverson GL. Systematic review of multivariable prognostic models for mild traumatic brain injury. Journal of neurotrauma. 2015;32(8):517-26.

164. Faux S, Sheedy J, Delaney R, Riopelle R. Emergency department prediction of post-concussive syndrome following mild traumatic brain injury--an international cross-validation study. Brain Inj. 2011;25(1):14-22.

165. Ingebrigtsen T, Waterloo K, Marup-Jensen S, Attner E, Romner B. Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. Journal of neurology. 1998;245(9):609-12.

166. Stulemeijer M, van der Werf S, Borm GF, Vos PE. Early prediction of favourable recovery 6 months after mild traumatic brain injury. Journal of neurology, neurosurgery, and psychiatry. 2008;79(8):936-42.

167. van der Naalt J, Timmerman ME, de Koning ME, van der Horn HJ, Scheenen ME, Jacobs B, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. The Lancet Neurology. 2017;16(7):532-40.

168. Lingsma HF, Yue JK, Maas AI, Steyerberg EW, Manley GT. Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. Journal of neurotrauma. 2015;32(2):83-94.

169. Szymanowicz D, Ciuffreda KJ, Thiagarajan P, Ludlam DP, Green W, Kapoor N. Vergence in mild traumatic brain injury: a pilot study. Journal of rehabilitation research and development. 2012;49(7):1083-100.

170. Johnson B, Hallett M, Slobounov S. Follow-up evaluation of oculomotor performance with fMRI in the subacute phase of concussion. Neurology. 2015;85(13):1163-6.